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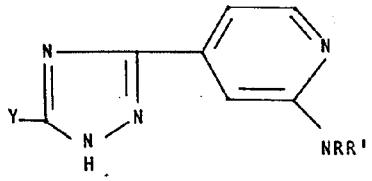
## (54) Triazole gastric anti-secretory agents.

(57) Gastric anti-secretory agents of the formula



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or pharmaceutically acceptable salts thereof, wherein R is alkyl and R' is hydrogen, methyl or ethyl; and

Y is hydrogen, hydroxymethyl, alkyl or $-(CH_2)_nNHC(Z)Q$ wherein n is an integer from 1 to 4; and

Z and Q, when taken together, form a 4-pyrimidinone group; or when taken separately, Z is oxygen, sulfur, $=N-C\equiv N$, or $=(CH)NO_2$; and Q is $-CH=CHR''$ wherein R'' is 2-methyl-5-thiazolyl, 4-pyridyl or 4-imidazolyl; or

Q is $-(CH_2)_mR'''$, wherein R''' is hydrogen, alkyl, thioalkoxy, alkoxy, amino, N-monoalkylamino, N,N-dialkylamino, 2-guanidino-4-thiazolyl, 5-dimethylaminomethyl-2-furyl, 2-pyrazinyl, 4-imidazolyl, 5-methyl-4-imidazolyl, phenyl, mono-substituted phenyl, 3-pyridyl, mono-substituted 3-pyridyl, 4-pyridyl, or mono-substituted 4-pyridyl, wherein said substituents are halo, alkoxy, hydroxy or alkylamino; and

m is 0 or an integer from 1 to 3;

provided that when R''' is hydrogen, alkoxy, phenoxy or pyridoxy, m is other than 0; said alkyl, alkoxy, and thioalkoxy groups having from 1 to 4 carbon atoms.

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P.C. 6436

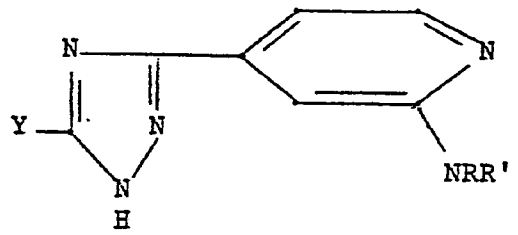
# TRIAZOLE GASTRIC ANTI-SECRETORY AGENTS

This invention relates to a series of novel 3'-substituted-5'-(2-amino-4-pyridyl)-1',2',4'-triazoles and their pharmaceutically acceptable salts which are antagonists of the $H_2$ histamine receptor and are therefore useful in the control of gastric secretion.

One of the known physiological effects of histamine is the stimulation of gastric acid secretion. It has been reported that a specific histamine receptor, the $H_2$ histamine receptor, mediates the stimulatory action of histamine (Black et al., Nature, 1972, 236, 385). Accordingly, an extensive search has been undertaken for agents which block the $H_2$ receptor and thus inhibit gastric acid secretion.

Durant et al. in U.S. Nos. 3,905,984 and 4,027,026 disclose that pyridyl substituted thioalkyl, oxyalkyl thiourea and oxyalkyl urea are inhibitors of histamine activity and the $H_2$ histamine receptors. Durant et al. in U.S. Nos. 4,022,797 and 4,024,271 disclose that thioalkyl aminoalkyl and oxyalkyl guanidines are likewise inhibitors of histamine activity. It has recently been disclosed by Lipinski in U.S. Patent No. 4,276,297 that a series of novel 5'-(4-pyridyl)-1',2',4'-triazole derivatives are inhibitors of the $H_2$ histamine receptor and are useful anti-ulcer agents.

The present invention relates to novel 3'-substituted-5'-(2-amino-4-pyridyl)-1',2',4'-triazoles useful as histamine $H_2$ antagonists which are anti-secretory agents and are therefore useful in the treatment of peptic ulcers and other conditions caused by or aggravated by gastric hyperacidity. More specifically, the novel compounds of this invention are those of Formula I



I

wherein R is alkyl; R' is hydrogen, methyl or ethyl; and

Y is hydrogen, hydroxymethyl, alkyl or

$$-(CH_2)_nNHC(Z)Q$$

wherein n is an integer from 1 to 4;

Z and Q when taken together, form a 4-pyrimidinone group; or when taken separately, Z is oxygen, sulfur, =N-C≡N or =(CH)$NO_2$; and Q is -CH=CHR" wherein R" is 2-methyl-5-thiazolyl, 4-pyridyl or 4-imidazolyl; or

Q is $-(CH_2)_mR"'$

wherein R"' is hydrogen, alkyl, thioalkoxy, alkoxy, amino, N-monoalkylamino, N,N-dialkylamino, 2-guanidino-4-thiazolyl, 5-dimethylaminomethyl-2-furyl, 2-pyrazinyl, 4-imidazolyl, 5-methyl-4-imidazolyl, phenyl, mono-substituted phenyl, 3-pyridyl; mono-substituted 3-pyridyl, 4-pyridyl, or mono-substituted 4-pyridyl, wherein said substituents are halo, alkoxy, hydroxy or alkylamino; and

m is 0 or an integer from 1 to 3;

provided that when R"' is

hydrogen, alkoxy, phenoxy or pyridoxy, m is other than 0; said alkyl, alkoxy and thioalkoxy groups having from 1 to 4 carbon atoms.

One group of compounds of interest are those wherein Y is hydrogen, hydroxymethyl, or alkyl. Preferred compounds include those wherein R is methyl or ethyl, R' is hydrogen and Y is hydrogen, methyl, ethyl or hydroxymethyl.

Another group of compounds of the present invention are those wherein Y is a group of the structure

$$-(CH_2)_nNHC(O)Q$$

wherein n is an integer from 1 to 4, including those wherein Q is alkyl, amino, methylamino, 2-guanidino-4-thiazolyl, 5-dimethylaminomethyl-2-furyl, 2-pyrazinyl, phenyl, substituted phenyl, 3-pyridyl, mono-substituted 3-pyridyl, 4-pyridyl or mono-substituted 4-pyridyl wherein said substituents are halo, alkoxy, hydroxy or alkylamino.

Preferred compounds include those wherein R is ethyl, R' is hydrogen, n is 2 and Q is methyl, ethyl, hydroxy-3-pyridyl, methoxyphenyl, amino, 2-N-ethylamino-4-pyridyl, 3-pyridyl, 5-dimethylaminomethyl-2-furyl, or 2-guanidino-4-thiazolyl.

Included in this group are compounds wherein Q is -CH=CHR" wherein R" is 2-methyl-5-thiazolyl, 4-pyridyl or 4-imidazolyl. Preferred compounds include those wherein R is ethyl, R' is hydrogen and n is 2.

Also included in this group are compounds wherein Q is $-(CH_2)_mR"'$ particularly those wherein R"' is

alkoxy, phenoxy, 3-pyridyloxy, 3-pyridyl, 4-pyridyl, phenyl, 4-imidazolyl or 5-methyl-4-imidazolyl and m is an integer from 1 to 3.

Preferred compounds include compounds wherein R is ethyl, R' is hydrogen, n is 2 and when m is 1, R"' is methoxy, phenoxy, 3-pyridyloxy, 4-pyridyl, when m is 2, R"' is phenyl, 3-pyridyl, or when m is 3, R"' is 4-imidazolyl or 5-methyl-4-imidazolyl.

Another group of compounds embraced by the present invention are those wherein Y is a thioureidoalkyl group of the structure

$$-(CH_2)_nNHC(S)Q$$

especially wherein Q is N-alkylamino. Preferred compounds include those wherein R is ethyl, R' is hydrogen, n is 2 to 4 and, Q is N-methylamino.

Another group of compounds of the present invention are guanidino alkyl compounds wherein Y is a group of the structure

$$-(CH_2)_nNHC(NCN)Q$$

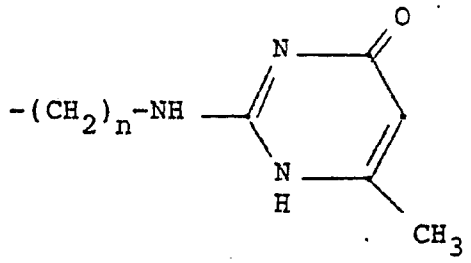
particularly wherein Q is N-lower alkylamino, N,N-di-lower alkylamino, or thioalkoxy. Preferred compounds include those wherein R is ethyl, R' is hydrogen, n is 2, and Q is N-methylamino or N,N-dimethylamino.

Another group of compounds of the present invention are nitroethylenediaminoalkyl compounds wherein Y is a group of the structure

$$-(CH_2)_nNHC(CHNO_2)Q$$

wherein Q is N-lower alkylamino. Preferred compounds include those wherein R is ethyl, R' is hydrogen, n is 2 and Q is N-methylamino.

A further group of compounds embraced by the present invention are those wherein Y is a 4-hydroxy-2-pyrimidylaminoalkyl group of the structure

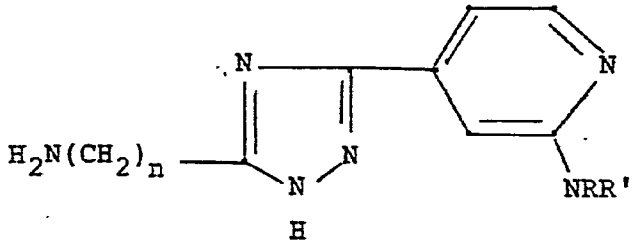


Preferred compounds include those wherein R is ethyl, R' is hydrogen and n is 2.

Also embraced by the present invention are pharmaceutical compositions comprising a gastric anti-secretory effective amount of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier or diluent. Preferred pharmaceutical compositions are those containing the preferred compound of Formula I as described hereinabove.

The present invention also comprises a method of treating gastric hyperacidity in an animal in need of treatment comprising administering to the animal a gastric anti-secretory effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. Preferred compounds for use in this method of treatment are the preferred compounds of Formula I as described hereinabove.

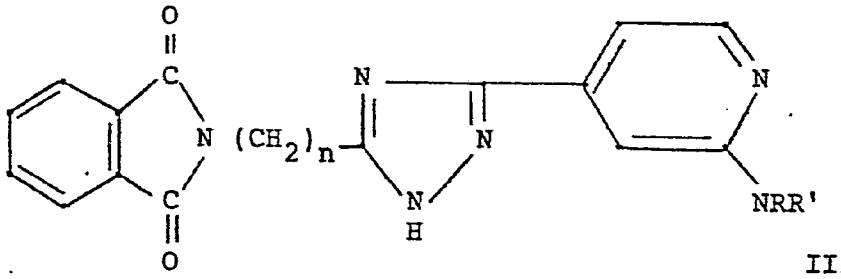
The present invention also includes novel intermediates useful in the preparation of the compounds of Formula I. More particularly, such compounds are those of Formula II



II

and the acid addition salts thereof, wherein n is an integer from 1 to 4, R is alkyl of 1 to 4 carbon atoms and R' is hydrogen, methyl or ethyl.

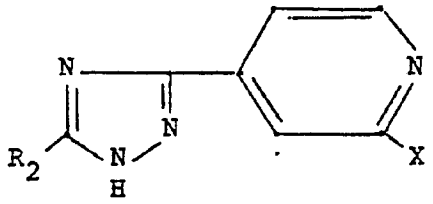
Further intermediates useful for the preparation of compounds of Formula I are those of Formula III



III

wherein n is an integer from 1 to 4, preferably 2, R is alkyl of 1 to 4 carbon atoms and R' is hydrogen, methyl or ethyl.

Further intermediates useful for the preparation of compounds of Formula I are those of Formula IV

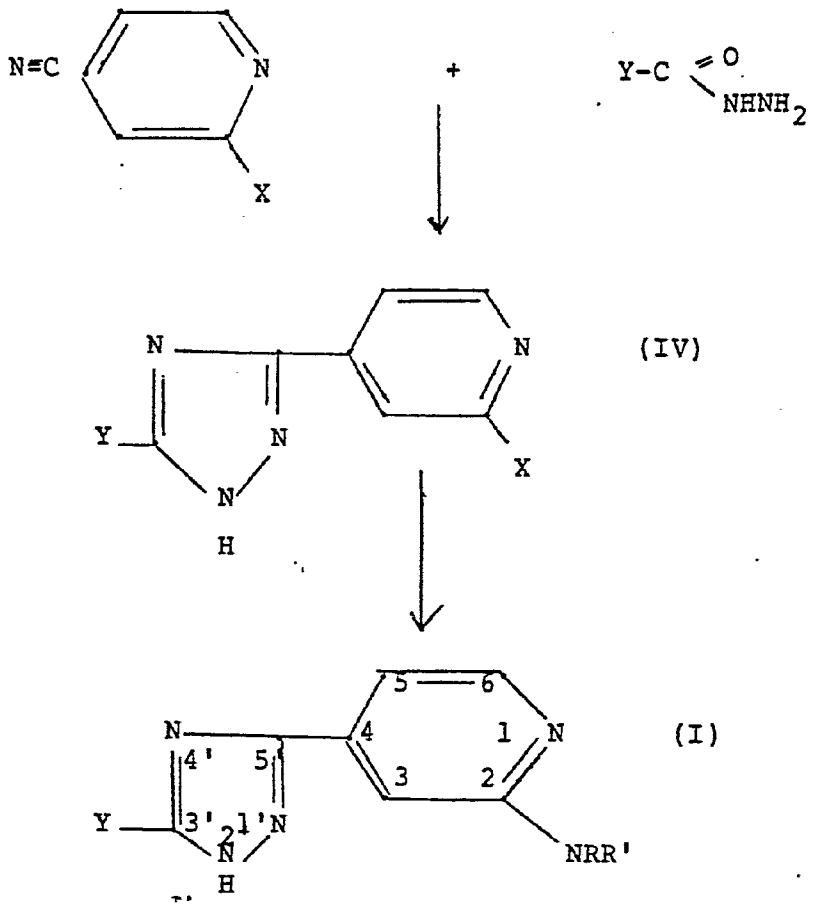


IV

and the acid addition salts thereof wherein $R_2$ is hydrogen, alkyl of 1 to 4 carbon atoms or hydroxyalkyl of 1 to 4 carbon atoms and X is halo, preferably chloro.

The novel compounds of Formula I wherein Y is hydrogen, alkyl or hydroxyalkyl may be prepared by the reaction sequence shown in Scheme I. The numbering of the two heterocyclic rings in Scheme I is that employed throughout the specification.

Scheme I

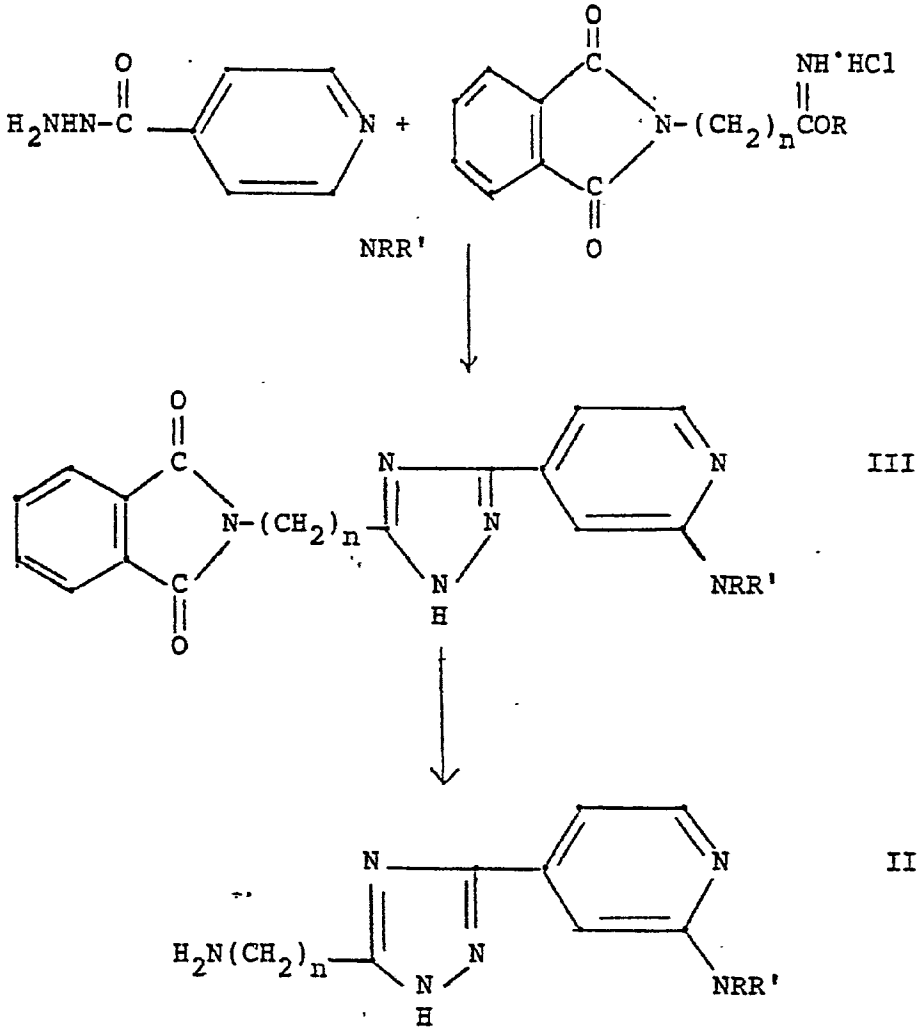


In Scheme I, a 2-haloisonicotinonitrile is treated with an alkali metal alkoxide such as sodium methoxide in an alcohol solvent such as methanol at a temperature between 15° to 35°C and then allowed to react with an essentially equimolar amount of an appropriate carboxylic acid hydrazide in a suitable solvent, preferably methanol under reflux for about 20 hours. If necessary, as in the case of the 3-hydroxymethyl derivative, the pH is maintained between 9-10 during reflux by addition of dilute base, e.g. alkali metal hydroxide preferrably sodium hydroxide. It will be understood that in the resulting compound, an intermediate of Formula IV, the substituent at the 3 position is determined by the particular acid hydrazide employed in the synthesis. Thus for example acetic acid hydrazide is employed to produce 3'-methyl-5'-(2-halo-4-pyridyl)-1',2',4'-triazole, formic acid hydrazide to produce 3-(2-halo-4-pyridyl)-1',2',4'-triazole, propionic acid hydrazide to produce 3'-ethyl-5'-(2-halo-4-pyridyl)-1',2',4'-triazole and glycolic acid hydrazide to produce 3'-hydroxymethyl-5'-(2-halo-4-pyridyl)-1',2',4'-triazole.

This halo intermediate of Formula IV is finally converted to an amino derivative of Formula I by heating with an appropriate aqueous alkylamine solution at about 160°C to 180°C for about 20 hours. For example, the preferred compounds of Formula I in which R is ethyl and R' is hydrogen may be prepared from the halo intermediate of Formula IV and aqueous ethylamine at about 160°C to 180°C for 16 to 18 hours.

In a second reaction sequence, illustrated by Scheme II, compounds of Formula I of the present invention may be prepared from intermediate compounds of Formula II which may be prepared from compounds of Formula III.

Scheme II

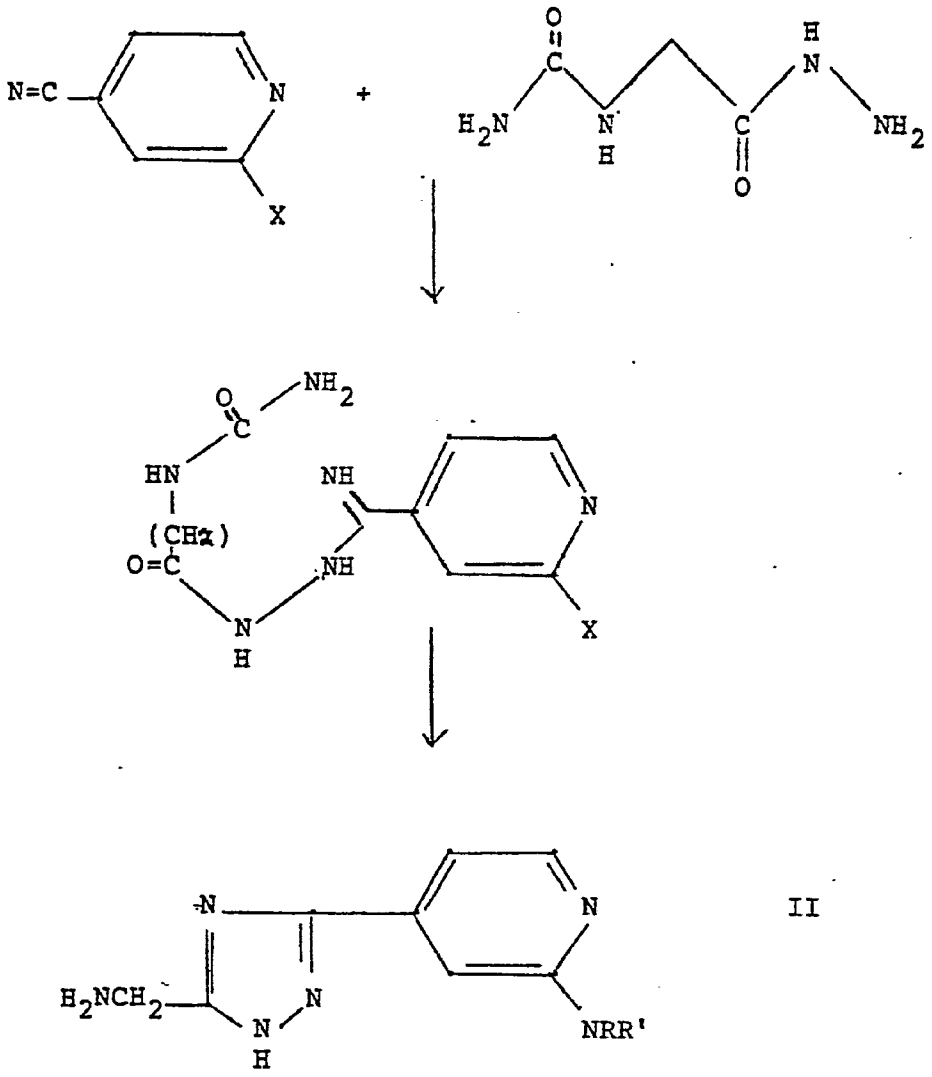


In Scheme II, an alkyl-3-phthalimido-alkanimidate salt, preferably ethyl-3-phthalimido-propionimidate hydrohalide prepared from 3-phthalimido propionitrile by standard procedures well-known in the art, is allowed to react with an equimolar amount of alkali metal alkoxide, preferably sodium ethoxide in an alcohol, preferably ethanol, and is then combined with a 2-alkylamino isonicotinic acid hydrazide, preferably 2-ethylamino isonicotinic acid hydrazide. Reaction is continued under reflux, for example, for 16 hours to 48 hours to produce 3'-(phthalimidoalkyl)-5'-(2-alkyl substituted-4-pyridyl)-1',2',4'-triazole, an intermediate compound of Formula III.

This intermediate may be subsequently converted to the intermediate of Formula II by an excess molar amount of hydrazine hydrate in a polar reaction inert solvent such as an alkyl alcohol, preferably ethanol, and heated at about 75° to 100°C for about 2 hours. The product, a 3'-(aminoalkyl)-5'-(2-alkylamino-4-pyridyl)-1',2',4'-triazole, is recovered as the addition salt by crystallization from mineral acid.

An alternative preparation for compounds of Formula II again utilizing as starting reagent a 2-halo-isonicotinonitrile, is given in Scheme III.

Scheme III




II

In Scheme III, a 2-haloisonicotinonitrile, preferably the chloro derivative, is combined with a less than equimolar amount of an alkali metal lower alkoxide, preferably sodium methoxide or sodium ethoxide in an alkyl alcohol. The solution is stirred for about 2 hours at about 15°C to 30°C, an equimolar amount of hydantoic acid hydrazide is added and the solution is heated at reflux for up to several days, when the resultant N-(2-halo-isonicotinimidoyl)-N'-ureidomethyl carbonyl hydrazine hydrate is formed. It is then combined with an aqueous alkylamine and heated under pressure at about 150 to 190°C for up to several days to produce 3'-aminomethyl-5'-(2-alkylamino-4-pyridyl)-1',2',4',-triazole hydrochloride, an intermediate compound of Formula II.

The novel compounds of Formula I wherein Y is an amide of the structure

$$-(CH_2)_n\overset{\overset{O}{\|}}{\underset{H}{N}}CQ$$

may be prepared from intermediate amino compounds of Formula II by three alternative methods.

In a first method, wherein Q is alkyl, phenyl, mono-halo substituted phenyl, or alkyl substituted with methoxy, phenoxy or phenyl, may be prepared by combining an appropriate intermediate of Formula II

with an excess molar amount of a trialkylamine and an essentially equimolar amount of carboxylic acid halide, preferably an acid chloride, of the formula QC(O)Cl in a suitable reaction inert solvent such as pyridine. The reaction solution is stirred at room temperature until reaction is complete, up to several days. Thus, for example, the preferred compounds wherein n is 2, R is ethyl, R' is hydrogen and Q is methyl, ethyl, isopropyl, methoxy methyl, phenoxy methyl, phenyl, chlorophenyl or phenylethyl may be prepared by combining 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole bis hydrochloride in dry pyridine with an essentially equimolar amount of triethylamine followed by an essentially equimolar amount of the corresponding carboxylic acid chloride of formula QC(O)Cl.

A second method for preparation of the novel amido derivatives of the present invention comprises combining

1,1'-carbonyl diimidazole in a reaction inert solvent such as tetrahydrofuran or acetonitrile with a carboxylic acid of the structure QCOOH. After heating at reflux, an equimolar amount of an appropriate 3'-(2-aminoalkyl)-5'-(2-alkylamino-4-pyridyl)-1',2',4'-triazole, Formula II, is added and reflux is continued until reaction is complete, for example from one to 20 hours. Preferred compounds which may be prepared by this method include those in which R is ethyl, R' is hydrogen, n is 2 and Q is pyridyloxymethyl, pyridylmethyl, methoxynicotinyl, hydroxynicotinyl, pyridinyl, methoxyphenyl, ethylaminoisonicotinyl, dimethylaminomethylfuryl, guanidino-4-thiazolyl, 3-pyridylethyl, 4-pyridylethyl, 4-pyridylmethyl, 4-imidazolylpropionyl, 4-imidazolyl ethyl, 4-pyridyl ethenyl and guanidinothiazolyl.

A third preparative method for novel amido derivatives of the present invention comprises combining a carboxylic acid QCOOH in a suitable solvent such as methylene chloride at about -10°C to 10°C with an essentially equimolar amount of a

trialkylamine and an essentially equimolar amount of an alkyl chloroformate and, after stirring for about one-half hour near 0°C adding an essentially equimolar amount of an appropriate 3'-(aminoalkyl)-5'-(2-alkylamino-4-pyridyl)-1',2',4'-triazolee, Formula II. The solution is stirred at 15° to 35°C for about 12 to 48 hours.

For example, preferred compounds of the present invention which may be prepared by this method include those in which R is ethyl, R' is hydrogen, n is 2 and Q is 4-pyridyl or 3-pyridyl.

Compounds of Formula I of the present invention wherein Y is an alkyl urea derivative of the structure

$$-(CH_2)_n NHCNHR_3$$

wherein n is an integer from 1 to 4, and $R_3$ is hydrogen or alkyl may be prepared from an intermediate compound of Formula II and an appropriate isocyanate. For example, the preferred compounds N-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))-ethyl)-N'-methylurea, wherein n is 2, R is ethyl, R' is hydrogen and $R_3$ is hydrogen may be prepared by dissolving a 3'(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole, of Formula II, in an essentially equimolar amount of aqueous acid, preferably hydrochloric acid, followed by addition of an essentially equimolar amount of an alkali metal isocyanate, preferably potassium or sodium isocyanate. Reaction is continued with stirring near room temperature for about 18 to 48 hours. A second preferred compound, N-(2-(3'-(4'-(2-ethylamino-4-

pyridyl)-1',2',4'-triazolyl))ethyl)-N'-methyl urea wherein $R_3$ is methyl may be prepared similarly by heating a 3'(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole of Formula II and an essentially equimolar amount of aqueous acid, preferably hydrochloric acid, with an excess molar amount of methyl isocyanate at about 90°C for about 1 to 4 hours.

Compounds of Formula I of the present invention wherein Y is thiourea derivative of the structure

$$-(CH_2)_n-NH-\overset{\overset{S}{\|}}{C}-NHR_4$$

wherein n is an integer from 1 to 4 and $R_4$ is alkyl, may be prepared from intermediate compounds of Formula II by addition of an excess molar amount of an appropriate alkyl isothiocyanate in a polar solvent such as water followed by heating at reflux for about 12 to 24 hours. For example, a preferred compound N-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))-ethyl)-N'-methylthiourea may be prepared by combining 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole hydrochloride and an excess molar amount of methyl isothiocyanate in the presence of a base such as an alkali metal carbonate, preferably potassium carbonate, in water and heating at reflux for about three hours.

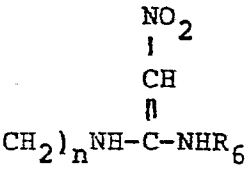
Compounds of Formula I of the present invention wherein Y is N-alkylcyanoguanidino or N,S-dialkyl-N-cyanoisothiourea of the formula

$$-(CH_2)_nNH-\overset{\overset{N}{\|}}{\underset{\underset{N}{\|}}{C}}-R_5$$

wherein n is an integer from 1 to 4 and $R_5$ is S-alkyl, N-alkyl or N,N-dialkyl may be prepared by treating an intermediate compound of Formula II with an equimolar amount of an alkali metal carbonate, preferably potassium carbonate in a suitable solvent such as aqueous ethanol, for about 1 to 2 hours followed by addition of an essentially equimolar amount of an appropriate di-alkyl cyanodithio-imino carbonate at room temperature for about 24 to 48 hours. Thus, for example, a compound wherein $R_5$ is S-methyl may be prepared by this method from an intermediate compound of Formula II and dimethyl cyanodithioimino carbonate.

This novel S-methyl compound may be further converted to a cyanoguanidino compound of Formula I by treatment with an appropriate aqueous alkylamine at about 70°C for about 24 to 90 hours. Thus, for example, N-cyano-N',N'-dimethyl-N"-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethyl)guanidine, a preferred compound of the present invention, wherein $R_5$ is N,N-dimethylamino may be prepared in this manner by treatment of the S-methyl-N-cyanoisothiourea derivative with aqueous dimethylamine. Likewise N-cyano-N'-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))-ethyl)-N"-methyl-guanidine is prepared from the S-methyl-N-cyanoisothiourea and aqueous methylamine.

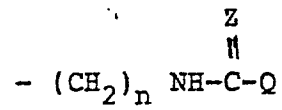
Compounds of Formula I of the present invention wherein Y is of the structure



wherein n is an integer from 1 to 4 and $R_6$ is alkyl, may be prepared by adding to compounds of Formula II an equimolar amount of N-alkyl-1-alkylthio-2-nitroethene-amine in an alkyl alcohol, preferably ethanol or isoamyl alcohol, and heating at reflux, for example for about 20 hours to 48 hours.

For example, preferred compounds wherein n is 2 and $R_6$ is methyl, may be prepared from 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole and N-methyl-1-methylthio-2-nitro-ethenamine.

The compounds of Formula I of the present invention wherein Y is



wherein Z and Q together form a 4-pyrimidinone group may be prepared by combining an intermediate compound of Formula II with an equimolar amount of 2-methylthio-6-methyl-pyrimidin-4-one and heating at about 100°

to 200°C for about two hours until gas evolution ceases.

The pharmaceutically acceptable acid addition salts of the novel compounds of Formula I and the corresponding salts of the intermediates of Formulae II and III are also embraced by the present invention. The salts may be readily prepared by contacting the free base with an appropriate mineral or organic acid in either aqueous solution or in a suitable organic solvent. The solid salt may then be obtained by precipitation or by evaporation of the solvent. The pharmaceutically acceptable acid addition salts of this invention include, but are not limited to, the hydrochloride, sulfate, bisulfate, mesylate, tosylate, nitrate, phosphate, acetate, lactate, maleate, fumarate, citrate, tartrate, succinate, gluconate and the like. Hydrochloride salts are preferred. If desired, the compounds of Formula I, II and III as the free base may be formed from the acid addition salts thereof by treatment with an appropriate base followed by extraction of the free base with a suitable organic solvent.

The compounds of Formula I and the pharmaceutically acceptable acid addition salts thereof have activity as antisecretory agents and histamine $H_2$ antagonists and accordingly are of therapeutic value in the treatment of gastric hyperacidity and peptic ulcers. For the purposes of the present specification and claims hereof the term treatment of gastric hyperacidity is meant to include the treatment of peptic ulcers and other such conditions caused by, or aggravated, by the secretion of gastric acid. The compounds may be administered to a subject in

need of treatment by a variety of conventional routes of administration including orally, intravenously and parenterally. Preferably, the compounds are administered orally. In general, these compounds will be administered orally at one or more doses between about 2 to 20 mg/kg body weight of the subject to be treated per day, preferably from about 500 to 2000 mg per day. If parenteral or intravenous administration is desired, then these compounds can be given at doses between about 1 to 20 mg/kg body weight of the subject to be treated per day. However, some variation in dosage will necessarily occur depending upon the condition of the subject being treated and the particular compound employed.

The compound may be administered alone or in combination with pharmaceutically acceptable carriers or diluents, in either single or multiple doses. Suitable pharmaceutical carriers include inert diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed by combining the novel compounds of Formula I or salts thereof and pharmaceutically acceptable carriers are readily administered in a variety of dosage forms such as tablets, powders, capsules, lozenges, syrups and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for oral administration, tablets containing various excipients, such as sodium citrate, may be employed, together with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia.

Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Preferably, the novel compounds of this invention are administered orally in unit dosage form, i.e. as a single physically discrete dosage unit containing an appropriate amount of the active compound in combination with a pharmaceutically acceptable carrier or diluent. Examples of such unit dosage forms are tablets or capsules containing from about 100 to 500 mg of the active ingredient, the compound of Formula I comprising from about 50% to 90% of the total weight of the dosage unit.

For parenteral administration, solutions of the compounds of Formula I in sterile aqueous solutions, for example aqueous propylene glycol, sodium chloride, dextrose or sodium bicarbonate solutions may be employed. Such solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The preparation of suitable sterile liquid media for parenteral administration will be well-known to those skilled in the art.

The activity of the compounds of the present invention as antisecretory agents and histamine-$H_2$ antagonists may be determined by standard pharmacological tests, including for example (1) measuring their ability to antagonize the actions of histamine which are not blocked by an antihistamine such as mepyramine and (2) measuring their ability to inhibit gastric acid secretion in the stomachs of Heidenhain pouch dogs that had previously been treated with pentagastrin in order to stimulate the secretion of gastric acid.

The present invention is illustrated by the following examples. However, it should be understood that the invention is not limited to the specific details of these examples. All temperatures are in degrees centigrade.

Example 1

3'-Methyl-5'-(2-chloro-4-pyridyl)-1',2',4'-triazole

This example illustrates the preparation of an intermediate of Formula IV.

6.9 g (49.8 mmol) of 2-chloroisonicotinonitrile was stirred with sodium methoxide (5.2 mmol) from 120.2 mg of sodium in 100 ml of methanol. After one hour at 25°C, 3.7 g (49.9 mmol) of acetic acid hydrazide was added to give after several minutes a clear solution. The reaction was heated at reflux for 20 hours at which time a precipitate began to form. Reflux was continued for an additional 120 hours during which time the reaction precipitate went into solution. The reaction was cooled and the initially formed precipitate was removed by filtration. The mother liquors were concentrated in vacuo with formation of a second precipitate. This was collected by filtration and dried to give 1.8 g (19%) of 3'-methyl-5'-(2-chloro-4-pyridyl)-

1',2',4'-triazole mp 215-218°C.

Anal. $C_8H_7ClN_4$. Calcd: C, 49.37; H, 3.63; N, 28.79; Cl, 18.22. Found: C, 49.22; H, 3.84; N, 28.35; Cl, 17.74.

Example 2

3'-Methyl-5'-(2-methylamino-4-pyridyl)-1',2',4'-triazole

5.3 g (27.23 mmol) of 3'-methyl-5'-(2-chloro-4-pyridyl)-1',2',4'-triazole (preparation given in Example 1) was combined with 50 ml of 40% aqueous methylamine solution in a 150 ml stainless steel reaction vessel and heated at 170°C for 21 hours. After cooling in ice, the contents of the reaction vessel were concentrated in vacuo to an orange oil from which a solid began to crystallize. The crude oily solid was slurried in ethylacetate-methanol and the resulting off-white solid was collected by filtration and dried in vacuo to give 2.1 g of crude product. This material was taken up and recrystallized from ethylacetate-methanol. Upon concentration and cooling 211 mg of material mp 294-295°C was collected. On standing the mother liquors deposited 395 mg (7%) of 3'-methyl-5'-(2-methylamino-4-pyridyl)-1',2',4'-triazole, mp 208-210°C. NMR ($Me_2SO$) $\delta$ 7.98 (d, 1H), 7.05 (m, 3H), 2.86 (broad s, 3H), 2.42 (s, 3H).

Example 3

3'-Methyl-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole

1.6 g (8.22 mmol) of 3'-methyl-5'-(2-chloro-4-pyridyl)-1',2',4'-triazole (preparation given in Example 1) was combined with 50 ml of 70% aqueous ethylamine and placed in a 150 ml stainless steel reaction vessel and heated at 170°C for 16.5 hours. Using a similar procedure, 4.4 g (22.61 mmol) of 3'-methyl-5'-(2-chloro-4-pyridyl)-1',2',4'-triazole was combined with 50 ml of 70% aqueous ethylamine and heated at 170°

for 16.5 hours. On cooling, the contents of the reaction vessels were combined and concentrated in vacuo to a crude brown solid. Water was removed by repeatedly concentrating in vacuo with methanol to give a crude brown solid. This material was crystallized from acetonitrile-ethanol to give a pale brown solid mp 223-227°C. This material was recrystallized from acetonitrile-ethanol to give 1.636 g (26%) of 3'-methyl-5'-(2-ethyl-amino-4-pyridyl)-1',2',4'-triazole as an off-white solid, mp 226-228°C; NMR ($Me_2SO$) $\delta$ 8.03 (1H, d), 7.03(2 H, m), 6.57 (1H, t), 3.33 (2H, m), 2.43 (3H, s), 1.17 (3H, t).

Anal. $C_{10}H_{13}H_5$. Calcd: C, 59.09; H, 6.45; N, 34.46. Found: C, 58.76; H, 6.42; N, 34.48.

## Example 4

## 3'-(2-Chloro-4-pyridyl)-1',2',4'-triazole hydrate

This example illustrates the preparation of an intermediate compound of Formula IV.

6.9 g (49.8 mmol) of 2-chloroisonicotinonitrile was stirred with a catalytic amount of sodium methoxide (3.8 mol) from 86.4 mg of sodium in 100 ml methanol. Within 5 minutes all the isonicotinonitrile was in solution. After one hour at 25°C, 3.0 g (49.9 mmol) of formic acid hydrazide was added to give a clear solution. The solution was heated at reflux. After three hours a precipitate began to form. Reflux was continued for a total of 24 hours. The reaction was cooled and a yellow solid collected by filtration. The mother liquors were concentrated and a second solid precipitated. This material was collected to give 4.9 g (50%) of 3'-(2-chloro-4-pyridyl)-1',2',4'-triazole hydrate, mp 184-186°C.

Anal. $C_7H_5ClN_4 \cdot H_2O$, Calcd: C, 42.33; H, 3.55; N, 28.21. Found: C, 42.53; H, 3.74; N, 28.37.

Example 5

3'-(2-Ethylamino-4-pyridyl)-1',2',4'-triazole

4.8 g (26.58 mmol) of 3'-(2-chloro-4-pyridyl)-1',2',4'-triazole (preparation given in Example 4) was combined with 70 ml of 70% aqueous ethylamine and placed in a 150 ml stainless steel reaction vessel and heated at 170° for 18 hours. After cooling, the contents of the vessel were filtered and the filtrate evaporated to an orange oil. This material was chromatographed on 400 g silica gel using ethyl acetate as eluent to give 2.158 g (43%) of 3'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole as a creme colored solid, mp 153-155°C; NMR ($Me_2SO$) $\delta$ 8.38 (s, 1H), 7.93 (d, 1H), 6.95 (m, 2H), 6.53 (t, 1H), 3.25 (m, 2H), 1.13 (t, 3H).

Anal. $C_9H_{11}N_5$, Calcd: C, 57.12; H, 5.86; N, 37.02. Found: C, 56.56; H, 5.84; N, 36.58.

Example 6

3'-Ethyl-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole hemi-hydrate

5.0 g (36.08 mmol) of 2-chloroisonicotinonitrile was stirred in 100 ml of $CH_3OH$ with a catalytic amount of sodium methoxide (5.39 mmol) from 124 mg of sodium. After stirring for one hour at 25°C, 6.0 g (31.9 mmol) of propionic acid hydrazide was added and the reaction was heated at reflux for 40 hours. An additional portion of 3.3 g (17.5 mmol) of propionic acid hydrazide was added and reflux was continued for an additional 120 hours. The reaction was cooled and concentrated in vacuo to an orange oil which was triturated with an ether-ethylacetate-methanol mixture to remove a small quantity of yellow solid lacking an ultraviolet chromophore. The mother liquor was reconcentrated in vacuo to an orange oil and combined

with 75 ml of 70% aqueous ethylamine and placed in a 150 ml stainless steel reaction vessel and heated at 160° for 17 hours. After cooling, the reaction contents were concentrated in vacuo to a green oil which was triturated with an ethylacetate methanol mixture to remove a solid with no ultraviolet absorbance. The mother liquors were reconcentrated to an oil and chromatographed on silica gel using a 95:5 mixture of ethylacetate-methanol as eluent. In this manner was obtained 214.1 mg (2.6%) of 3-ethyl-5-(2-ethylamino-4-pyridyl)-1,2,4-triazole hemihydrate, mp 142-144°C; NMR ($CDCl_3$) $\delta$ 9.3 (broad s, 1H) 7.8 (d, 1H), 7.53-7.2 (m, 3H), 3.53 (s, 1H, 1/2 $H_2O$), 3.41 (m, 2H), 2.91 (q, 2H), 1.40 (t, 3H), 1.13 (t, 3H).

Anal. $C_{11}H_{15}N_5 \cdot 1/2\ H_2O$, Calcd: C, 58.38; H, 7.13; N, 30.95. Found: C, 58.07; H, 6.89; N, 30.62.

## Example 7

## 3'-Hydroxymethyl-5'-(2-chloro-4-pyridyl)-1',2',4'-triazole

This example illustrates the preparation of an intermediate compound of Formula IV.

23.5 g (169.6 mmol) of 2-chloroisonicotinonitrile was dissolved in 300 ml of methanol containing 21.7 mmol of sodium methoxide prepared from 500 mg sodium. After stirring one hour at 25°C, 15.3 g (169.6 mmol) of glycolic acid hydrazide was added and the reaction was heated at reflux for 2.5 hours. After cooling, the reaction was concentrated in vacuo and the methanol solvent was replaced by a solution of 1:1 dioxane-water. The reaction was heated to reflux and dilute NaOH solution was added periodically to maintain the pH at 9 to 10 over a period of 6 hours. While still hot, the reaction was filtered and the clear filtrate allowed to remain at 25°C over 60 hours. During this time there formed a precipitate of 17.6 g (49%)

3'-hydroxymethyl-5'-(2-chloro-4-pyridyl)-1',2',4'-triazole, mp 166-168°C. High resolution mass spectrum $C_8H_7N_4OCl$, $Cl^{37}$ isotope M/E Calcd. 212.0278. Found: 212.0274. $Cl^{35}$ isotope M/E Calcd. 210.0308. Found: 210.0311. NMR ($Me_2SO$) $\delta$ 8.43 (d, 1H), 7.87 (m, 2H), 4.67 (s, 2H).

Anal. $C_8H_7ClN_4O$, Calcd: C, 45.62; H, 3.35; N, 26.60. Found: C, 45.70; H, 3.67; N, 26.55.

Example 8

3'-Hydroxymethyl-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole

5.0 g (23.74 mmol) of 3'-hydroxymethyl-5'-(2-chloro-4-pyridyl)-1',2',4'-triazole (preparation given in Example 7) was combined with 100 ml of 50% aqueous ethylamine solution and heated at 180°C for 18 hours in a stainless steel reaction vessel. After cooling the contents were concentrated in vacuo and triturated with a methanol-ethylacetate mixture to give 3.6 g of a beige colored solid. This was recrystallized from methanol-ethylacetate to give 1.9 g (36%) of 3'-hydroxymethyl-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole, mp 226-228°C; NMR ($Me_2SO$) $\delta$ 7.93 (d, 1H), 6.97 (m, 2H), 6.47 (t, 1H), 4.6 (s, 2H), 3.27 (m, 2H), 2.83 (t, 3H).

Anal. $C_{10}H_{13}N_5O$, Calcd: C, 54.78; H, 5.98; N, 31.95. Found: C, 54.58; H, 6.15; N, 31.49.

Example 9

3'-(2-Phthalimidoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole

This example illustrates the preparation of an intermediate compound of Formula III.

18.7 g (66.1 mmol) of ethyl 3-phthalimidopropionimidate hydrochloride (prepared from 14.0 g (70.0 mmol) of 3-phthalimidopropionitrile) was reacted with 66.2 mmol of sodium ethoxide (from 1.52 g (66.2 mmol) of sodium pellets) in 225 ml of ethanol. The resultant slurry was filtered under nitrogen and to the clear

ethanol solution was added 12.5 g (69.3 mol) of 2-ethylaminoisonicotinic acid hydrazide. After heating at reflux for 16 hours, the reaction was filtered while still warm. The resultant solid was slurried in water and then refiltered and dried to give 12.4 g (52%) of 3'-(2-phthalimidoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole, mp 254-256°C.

Example 10

3'-(2-Aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole bishydrochloride

This example illustrates the preparation of an intermediate compound of Formula II.

11.85 g (32.7 mmol) of 3'-(2-phthalimidoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (preparation given in Example 9) was combined with 24 ml (49.05 mmol) of hydrazine hydrate in 200 ml ethanol and heated on a steam bath for 2 hours. The reaction changed from a slurry to an almost clear solution and back to a slurry during the course of the reaction. The reaction was cooled and filtered and the filtrate was concentrated in vacuo to a crude solid. This material was slurried in water and HCl added to pH 3. The slurry was refiltered and the filtrate concentrated in vacuo to a yellow solid. This material was recrystallized from methanol to give 3.46 g (34.7%) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole bishydrochloride, mp 260-261°C with decomposition. Concentration of the methanol mother liquors gave an additional 3.13 g (31.4%) of crude product; NMR ($D_2O$) $\delta$ 7.83 (d, 1H), 7.31 (m, 2H), 3.5 (m, 6H), 1.48 (t, 3H).

Anal. $C_{11}H_{16}N_6 \cdot 2HCl$, Calcd: C, 43.29; H, 5.94; N, 27.53. Found: C, 42.96; H, 5.98; N, 27.60.

Example 11

N-(4-Pyridylacryloyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl)) ethylamine

0.746 g (5.0 mmol) of 4-Pyridylacrylic acid and 0.811 g (5.0 mmol) of 1,1'-carbonyldiimidazole were combined in 25 ml tetrahydrofuran and heated at reflux until gas evolution ceased. 1.16 g (5.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole was added and the reaction was heated at reflux for 18 hours and concentrated in vacuo to an oil. Trituration with water gave a solid which was collected by filtration and recrystallization from methanol-water and again recrystallized from water to give 0.379 g (21%) of N-(4-pyridylacryloyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl-1',2',4'-triazolyl))ethylamine, mp 115°C; NMR ($Me_2SO$) $\delta$ 9.33 to 8.2 (m, 3H), 8.0 (d, 1H), 7.27 to 7.17 (m, 3H), 6.97 (m, 3H), 6.53 (t, 1H), 3.83 to 2.73 (m, 6H), 1.15 (t, 3H).

Example 12

N-[3-(2-methyl-5-thiazolyl)acryloyl]-2-[3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl)]ethylamine

To a mixture of 400 mg (2.36 mmol) of 3-(2-methyl-5-thiazolyl)acrylic acid in 40 ml of acetonitrile was added 383 mg (2.36 mmol) of 1,1'-carbonyldiimidazole and the mixture was heated at reflux under $N_2$ for 1 hour. To this was added 548 mg (2.36 mmol) of 3'-aminoethyl-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole and the mixture was heated at reflux for 19 hours. The mixture was cooled and the solid precipitate was collected by filtration, washed with acetonitrile, and dried to afford 310 mg (35%) of N-[3-(2-methyl-5-thiazolyl)acryloyl]-2-[3'-(5'-(2-ethylamine-4-pyridyl)-1',2',4'-triazolyl)]ethylamine, mp 239-241°. NMR (DMSO, $d_6$) $\delta$ 8.24 (broad t, 1H); 7.9-7.1 (m, 5H); 6.20 (d, 1H); 3.9-2.7 (m, 6H); 2.61 (s, 3H); 1.24 (t, 3H); ms:m/e = 383.

Example 13

N-Acetyl-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl)) ethylamine

600 mg (1.96 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole bishydrochloride (Example 10) was suspended in 7 ml of dry pyridine and 0.282 ml (4.13 mmol) of triethylamine was added to give a clear brown solution. 0.139 ml (2.16 mmol) of acetyl chloride was added and the reaction was stirred at 23°C for 20 hours. Methanol was added to the reaction and the solution was concentrated in vacuo. Sodium bicarbonate solution was added to the residue and the residue was reconcentrated in vacuo to a crude solid which was triturated with methanol and the methanol concentrated to a crude solid. This material was chromatographed on silica gel to give 370 mg (69%) of N-acetyl-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine as a glass-like solid. NMR ($Me_2SO$) $\delta$ 8.0 (d, 1H), 7.87 (broad s, 1H), 7.03 (m, 2H), 6.53 (t, 1H), 3.37 (m, 2H), 1.82 (s, 3H), 1.13 (t, 3H). Anal. $C_{13}H_{18}N_6O$, Calcd. C, 56.92; H, 6.61; N, 30.64. Found: C, 57.10; H, 6.73; N, 30.82.

Example 14

N-Propionyl-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine

600 mg (1.96 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole bishydrochloride (Example 10) was combined with 0.85 ml (6.09 mmol) of triethylamine and 0.179 ml (2.06 mmol) of propionyl chloride in 7 ml of dry pyridine. After stirring at 25°C for 20 hours, the reaction was diluted with water and extracted with ethylacetate. The ethylacetate extracts were dried over anhydrous sodium sulfate and concentrated to crude product. Recrystallization from acetonitrile gave 250 mg (44%) of N-propionyl-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine, mp 181-183°C.

NMR ($Me_2SO$) $\delta$ 7.93 (m, 2H), 7.03 (m, 2H), 6.55 (t, 1H), 3.37 (m, 4H), 2.97 (q, 2H), 2.1 (q, 2H), 1.07 (m, 6H).

Example 15

N-(2-Methylpropionyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1,2,4-triazolyl))ethylamine

600 mg (1.96 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole bishydrochloride (Example 10) was combined with 0.85 ml (6.09 mmol) of triethylamine and 0.216 ml (2.06 mmol) 2-methylpropionyl chloride in 7 ml of dry pyridine. After stirring for 60 hours the reaction was diluted with dilute aqueous sodium bicarbonate solution and extracted with ethylacetate. After drying over anhydrous sodium sulfate and concentration in vacuo, the crude product was crystallized from acetonitrile to give 300 mg (50%) of N-(2-methylpropionyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine, mp 181-183°C. NMR ($Me_2SO$) $\delta$ 7.87 (m, 2H), 6.97 (m, 2H), 3.36 (m, 4H), 2.9 (q, 2H), 2.27 (m, 1H), 1.1 (q, 3H), 1.05 (s, 6H). Anal. $C_{15}H_{22}N_6O$, Calcd. C, 59.58; H, 7.33; N, 27.80. Found: C, 59.39; H, 7.62; N, 27.65.

Example 16

N-Methoxyacetyl-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine

600 mg (1.96 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole bishydrochloride (Example 10) was combined with 0.85 ml (6.09 mmol) of triethylamine and 0.188 ml (2.06 mmol) of methoxyacetyl chloride in 7 ml dry pyridine. After stirring at 25°C for 20 hours, the reaction was diluted with dilute aqueous sodium bicarbonate solution and extracted with ethylacetate. After drying over anhydrous sodium sulfate the ethyl acetate solution was concentrated in vacuo to 438 mg crude product. This was recrystallized

from acetonitrile to give 230 mg (39%) of N-methoxyacetyl-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine, mp 162-164°C. NMR ($Me_2SO$) $\delta$ 7.97 (m, 2H), 7.03 (m, 2H), 6.53 (t, 1H), 3.83 (s, 2H), 3.67 to 2.67 (m, 6H), 3.3 (s, 3H), 1.15 (t, 3H).

Anal. $C_{14}H_{20}N_6O_2$, Calcd. C, 55.25; H, 6.62; N, 27.62. Found: C, 55.03; H, 6.67; N, 27.41.

Example 17

N-Phenoxyacetyl-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine hemihydrate

600 mg (1.96 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole bishydrochloride (Example 10) was combined with 0.85 ml (6.09 mmol) of triethylamine and 0.285 ml (2.06 mmol) of phenoxyacetyl-chloride in 7 ml dry pyridine and stirred for one hour at 25°C. The reaction was diluted with water and the pH adjusted to 8.5 with dilute aqueous sodium bicarbonate solution. Extraction with ethyl acetate, drying over anhydrous sodium sulfate and concentration in vacuo gave 748 mg of crude product. This material was crystallized from ethyl acetate to give 396 mg (54%) of N-phenoxyacetyl-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine hemihydrate, mp 150-152°C. NMR ($Me_2SO$) $\delta$ 8.28 (t, 1H), 8.05 (d, 1H), 7.47 to 6.77 (m, 7H), 6.6 (t, 1H), 4.53 (s, 2H), 3.83 to 2.8 (m, 6H), 1.23 (t, 3H).

Anal. $C_{19}H_{22}O_2N_6 \cdot 1/2\ H_2O$, Calcd. C, 60.78; H, 6.18; N, 22.38. Found: C, 61.12; H, 5.92; N, 22.24.

Example 18

N-Benzoyl-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine

600 mg (1.96 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole bishydrochloride

(Example 10) was combined with 0.85 ml (6.09 mmol) of triethylamine and 0.251 ml (2.16 mmol) of benzoylchloride in 10 ml of dry pyridine and stirred at 25°C for 4 hours. The reaction was diluted with methanol and concentrated in vacuo and diluted with water. Extraction with ethylacetate, drying over anhydrous sodium sulfate and concentration in vacuo gave 700 mg crude product. This was recrystallized from 10 ml acetonitrile to give 490 mg (74%) of N-benzoyl-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine, mp 160-168°C. NMR ($Me_2SO$) $\delta$ 8.17 to 7.43 (m, 7H), 7.07 (m, 2H), 6.56 (t, 1H), 3.67 to 2.53 (m, 6H), 1.17 (t, 3H).

Anal. $C_{18}H_{20}N_6O$, Calcd. C, 64.26; H, 5.99; N, 24.99. Found: C, 64.37; H, 5.67; N, 24.62.

Example 19

N-(4-Chlorobenzoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine

600 mg (1.96 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole bishydrochloride (Example 10) was combined with 0.85 ml (6.09 mmol) of triethylamine and 0.27 ml (1.96 mmol) of 4-chlorobenzoylchloride in 6 ml of dry pyridine and stirred at 25°C for 20 hours. The reaction was diluted with aqueous sodium bicarbonate solution and extracted with ethylacetate. The ethylacetate solution was dried over anhydrous sodium sulfate and concentrated in vacuo to a crude solid. This was recrystallized from ethylacetate-methanol to give 420 mg (58%) of N-(4-chlorobenzoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine, mp 208-210°C. NMR ($Me_2SO$) $\delta$ 8.71 (t, 1H), 8.0 (d, 1H), 7.65 (symmetrical m, 4H), 6.87 (m, 2H), 6.53 (t, 1H), 3.87 to 2.76 (m, 6H), 1.13 (t, 3H).

Anal. $C_{18}H_{19}ClN_6O$, Calcd. C, 58.30; H, 5.16; N, 22.66, Cl, 9.56. Found: C, 58.23; H, 5.28; N, 22.25; Cl, 9.68.

Example 20

N-(3-Phenylpropionyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine

600 mg (1.96 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole bishydrochloride (Example 10) was combined with 0.85 ml (6.09 mmol) of triethylamine and 0.33 ml (1.96 mmol) of 3-phenylpropionyl chloride in 6 ml of dry pyridine. After stirring several hours an additional 0.5 mmol of 3-phenylpropionyl chloride was added. After 20 hours at 25°C the reaction was diluted with aqueous sodium bicarbonate solution and extracted with ethylacetate. After drying over anhydrous sodium sulfate the ethylacetate was concentrated in vacuo to an oil which was chromatographed on silica gel using 7% methanol in chloroform as eluent to give 542 mg (76%) of N-(3-phenylpropionyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl)) ethylamine, mp 147-150°C. NMR ($Me_2SO$) $\delta$ 8.09 (d, 1H), 7.9 (t, 1H), 7.13 (broad s, 5H), 7.0 (m, 2H), 6.48 (t, 1H), 3.6 to 2.13 (m, 10H), 1.13 (t, 3H). Anal. $C_{20}H_{24}N_6O$, Calcd. C, 65.91; H, 6.64; N, 23.06. Found: C, 66.04; H, 6.29; N, 22.86.

Example 21

N-(3-Pyridyloxyacetyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine bishydrate

0.995 g (6.2 mmol) of 3-pyridyloxyacetic acid was slurried in 40 ml of tetrahydrofuran at 25°C to which was added 1.01 g (6.2 mmol) of 1,1'-carbonyldimidazole. The reaction was heated to reflux, gassing occurred and suspended material went into solution. When gassing stopped, 1.45 g (6.2 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was added. Reflux was continued for 45 minutes, the

yellow reaction solution was concentrated in vacuo to an oil and was triturated with water to give a crude solid. This was recrystallized from water and dried at 25°C to give 1.58 g (63%) of N-(3-pyridyloxyacetyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))-ethylamine bishydrate, mp 97-99°C. NMR ($Me_2SO$) $\delta$ 8.47 to 7.97 (m, 4H), 7.35 (m, 2H), 7.05 (m, 2H), 6.57 (t, 1H), 4.63 (s, 2H), 3.77 to 2.73 (m, 6H), 1.17 (t, 3H).

Anal. $C_{18}H_{21}N_7O_2 \cdot 2H_2O$, Calcd. C, 53.58; H, 5.76; N, 26.69. Found: C, 52.77; H, 6.28; N, 24.07. A sample dried at 78°C under high vacuum analyzed for anhydrous material.

Anal. $C_{18}H_{21}N_7O_2$, Calcd. C, 58.85; H, 5.76; N, 26.69. Found: C, 58.69; H, 5.67; N, 26.71.

Example 22

N-(4-Pyridylacetyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine

0.955 g (5.5 mmol) of 4-pyridylacetic acid hydrochloride was combined with 0.892 g (5.5 mmol) of 1,1'-carbonyldiimidazole in 25 ml of tetrahydrofuran and heated at reflux. After gassing had stopped the reaction was filtered to remove dark insoluble material and 1.16 g (5.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was added and the reaction heated at reflux for 20 hours. The reaction was concentrated in vacuo to an oil and twice slurried in ether. The ether solution containing imidazole was decanted from residual gummy material. This material was chromatographed on "Silica Gel 60" (E. M. Reagents) using 10% methanol in chloroform as eluent to give product as an oil which slowly solidified on standing. Trituration with ether-ethanol and filtration gave 340 mg (19%) of N-(4-pyridylacetyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-

triazolyl))ethylamine, mp 215-216°C. NMR ($Me_2SO$) δ 8.43 (d, 2 x 1H), 8.28 (t, 1H), 8.03 (d, 1H), 7.2 (d, 2H), 7.05 (d, 2H), 6.57 (t, 1H), 3.47 (s, 2H), 3.7 to 2.73 (m, 6H), 1.17 (t, 3H).

Example 23

N-(2-Methoxynicotinoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine

1.53 g (10.0 mmol) of 2-methoxynicotinic acid was dissolved in 25 ml of refluxing tetrahydrofuran and to the refluxing solution was added 1.78 g (11.0 mmol) of 1,1'-carbonyldiimidazole. The reaction was heated at reflux until gas evolution ceased and 2.32 g (10.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was added. After about 20 minutes at reflux a solid began to form. After one hour at reflux the solid was collected by filtration and the filtrate was concentrated in vacuo to an oily solid. This was triturated in water to give a solid which was collected by filtration. The combined solids were recrystallized from ethanol to give 1.64 g (45%) of N-(2-methoxynicotinoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))-ethylamine, mp 212-212.5°C. NMR ($Me_2SO$) δ 8.43 (t, 1H), 8.3 to 7.92 (m, 3H), 7.2 to 6.87 (m, 3H), 6.53 (t, 1H), 3.87 (s, 3H), 3.8 to 2.8 (m, 6H), 1.1 (t, 3H).
Anal. $C_{18}H_{21}N_7O_2$, Calcd. C, 58.85; H, 5.76; N, 26.69. Found: C, 58.42; H, 5.73; N, 26.30.

Example 24

N-(6-Hydroxynicotinoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine monohydrate

0.556 g (4.0 mmol) of 6-hydroxynicotinic acid was slurried in 25 ml of tetrahydrofuran and 0.713 g (4.4 mmol) of 1,1'-carbonyldiimidazole was added and the slurry was heated to reflux. Gas evolution

occurred but solution did not. After gas evolution stopped, 0.929 g (4.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was added to the refluxing slurry. Within 5 minutes solution occurred and reflux was continued for 20 hours. During this time a precipitate formed. This was collected by filtration and recrystallized from water to give 0.934 g (63%) of N-(6-hydroxynicotinoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))-ethylamine monohydrate, mp 157-159°C with decomposition; NMR ($Me_2SO$) $\delta$ 8.37 (t, 1H), 8.08 to 7.67 (m, 3H), 7.0 (m, 2H), 6.5 (t, 1H), 6.3 (d, 1H), 3.8 to 2.72 (m, 6H), 1.13 (t, 3H).

Anal. $C_{17}H_{19}N_7O_2 \cdot H_2O$, Calcd. C, 54.97; H, 5.70; N, 26.40. Found: C, 55.34; H, 5.66; N, 26.81.

Example 25

N-(2-Pyrazinoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine

0.621 g (5.0 mmol) of 2-pyrazinecarboxylic acid and 0.811 g (5.0 mmol) of 1,1'-carbonyldiimidazole was combined in 25 ml of tetrahydrofuran and heated at reflux. Solution gradually occurred and when gas evolution had ceased 1.16 g (5.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was added and reflux was continued for 18 hours. On cooling the tetrahydrofuran solution was decanted from a small amount of gummy residue and concentrated in vacuo to an oily solid. This material was then triturated in water and the resultant solid was collected by filtration and recrystallized from water containing a small amount of methanol to give 0.925 g (54%) of N-(2-pyrazinoyl--2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-

triazolyl))ethylamine, mp 211-213°C. NMR ($Me_2SO$) $\delta$ 9.24 (m, 1H), 9.16 (t, 1H), 8.90 (m, 1H), 8.74 (m, 1H), 8.07 (d, 1H), 7.13 (m, 2H), 6.6 (t, 1H), 4.03 to 2.9 (m, 6H), 1.2 (t, 3H).

Anal. $C_{16}H_{18}N_8O$, Calcd. C, 56.79; H, 5.36; N, 33.12. Found: C, 56.76; H, 5.33; N, 33.11.

Example 26

N-(3-Methoxybenzoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine

0.761 g (5.0 mmol) of 3-methoxybenzoic acid was combined with 0.811 g (5.0 mmol) of 1,1'-carbonyldiimidazole in 25 ml of tetrahydrofuran and heated at reflux until gas evolution ceased. 1.16 g (5.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was added and reflux was continued for 2 hours. The reaction was cooled and concentrated in vacuo to an oil. Trituration with water containing a small amount of methanol gave a solid which was recrystallized from water-methanol to give 900 mg (50%) of N-(3-methoxybenzoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl ethylamine, mp 139-141°C. NMR ($Me_2SO$) $\delta$ 8.57 (t, 1H), 8.02 (d, 1H), 7.53 to 6.87 (m, 6H), 6.53 (t, 1H), 3.8 (s, 3H), 3.73 to 2.83 (m, 6H), 1.17 (t, 3H).

Anal. $C_{19}H_{22}N_6O_2$, Calcd. C, 62.28; H, 6.05; N, 22.93. Found: C, 62.12; H, 6.40; N, 22.84.

Example 27

N-(2-Ethylaminoisonicotinoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine

0.83 g (5.0 mmol) of 2-ethylaminoisonicotinic acid was combined with 0.81 g (5.0 mmol) of 1,1'-carbonyldiimidazole in 20 ml of tetrahydrofuran and heated at reflux until gas evolution ceased. At this point some solid which still remained out of solution was

removed by filtration. 1.16 g (5.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was added and reflux was continued for 18 hours. The reaction was cooled and concentrated in vacuo to an oil which was triturated in water. The resulting solid was recrystallized from water to give 475 mg (25%) of N-(2-ethylaminoisonicotinoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))-ethylamine, mp 72-75°C. NMR ($Me_2SO$) $\delta$ 8.53 (t, 1H), 7.93 (d, 2 x 1H), 6.98 (m, 2H), 6.73 (m, 2H), 6.53 (t, 1H), 6.47 (t, 1H), 3.77 to 2.67 (m, 8H), 1.12 (t, 2 x 6H).

Example 28

N-(5-Dimethylaminomethyl-2-furoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl-1',2',4'-triazolyl))ethylamine

0.846 g (5.0 mmol) of 5-dimethylaminomethyl-2-furoic acid was combined with 0.811 g (5.0 mmol) of 1,1'-carbonyldiimidazole in 25 ml of tetrahydrofuran and heated at reflux until gas evolution ceased. 1.16 g (5.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was added and heating at reflux was continued for 18 hours. The reaction was concentrated in vacuo to an oil and triturated with ether. The ether was decanted and the remaining oil was chromatographed on "Silica Gel 60" (E. M. Reagents) and eluted with 10% methanol in chloroform to give 0.95 g (50%) of N-(5-dimethylaminomethyl-2-furoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl-1',2',4'-triazolylethylamine, mp 104-106°C. NMR ($Me_2SO$) $\delta$ 8.38 (t, 1H), 7.97 (d, 1H), 7.0 (m, 3H), 6.53 (t, 1H), 6.35 (d, 1H), 3.8 to 2.73 (m, 6H), 3.42 (s, 2H), 2.17 (s, 6H), 1.15 (t, 3H). High resolution mass spectrum ($C_{19}H_{25}N_7O_2$) M/E Calcd. 383.2070. Found 383.2040.

Example 29

N-(2-Guanidino-4-thiazoloyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl-1',2',4'-triazolyl))ethylamine

23.6 g (0.2 mol) of amidinothiourea was combined with 39.0 g (0.2 mol) of ethylbromopyruvate in 200 ml of ethanol and heated at reflux for 2 hours. The reaction was cooled and made basic with concentrated ammonium hydroxide. A solid formed and was collected by filtration, dried and recrystallized from a methanol-ethanol mixture to give 12.9 g (30%) of ethyl 2-guanidino-4-thiazolecarboxylate, mp 229-230°C with decomposition.

3.2 g (15 mmol) of ethyl-2-guanidino-4-thiazole-carboxylate was suspended in 25 ml of 3N potassium hydroxide solution and heated at reflux. After about 30 minutes at reflux solution occurred and after a total of one hour at reflux the reaction was cooled to 10°C and the pH was adjusted at 6 with concentrated hydrochloric acid. A solid formed and was collected by filtration and dried to give 3.0 g of crude 2-guanidino-4-thiazole carboxylic acid. NMR ($Me_2SO$) $\delta$ 7.23 (s, 1H), 7.13 (broad s, 4H).

1.87 g (10.0 mmol) of 2-guanidino-4-thiazole-carboxylic acid and 1.78 g (11.0 mmol) of 1,1'-carbonyldiimidazole were combined in 30 ml of tetrahydro-furan and heated at reflux until gas evolution ceased. Some material not in solution was removed by filtration. 1.16 g (5.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was added and the reaction was heated at reflux for 18 hours. A similar procedure was carried out using 0.931 g (5 mmol) of 2-guanidinothiazole-4-carboxylic acid, 0.811 g (5 mmol) of 1,1'-carbonyldiimidazole and 1.16 g (5.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-

1',2',4'-triazole. The oils resulting from concentration in vacuo of both runs were combined and chromatographed on "Silica Gel 60" (E. M. Reagents) using 10% methanol in chloroform as eluent to give 138 mg (14%) of N-(2-guanidino-4-thiazoloyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine, mp 150°C with decomposition; NMR ($Me_2SO$) $\delta$ 8.5 (t, 1H), 8.0 (d, 1H), 6.97 (s, 1H), 7.0 (m, 2H), 6.77 (broad s, 4H), 6.53 (t, 1H), 4.02 to 2.8 (m, 6H), 1.17 (t, 3H). High resolution mass spectrum ($C_{16}H_{20}N_{10}OS$) M/E Calcd. 400.1542. Found 400.1551.

Example 30

N-(4-Pyridylpropionoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine

0.756 g (5.0 mmol) of 4-pyridylpropionic acid and 0.811 g (5.0 mmol) of 1,1'-carbonyldiimidazole was combined in 15 ml of tetrahydrofuran and heated at reflux until gas evolution ceased. 1.16 g (5.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was added and the reaction was heated at reflux for 18 hours and concentrated in vacuo to an oil. Chromatography on "Silica Gel 60" (E. M. Reagents) using 10% methanol in chloroform as eluent gave product as an oil which solidified on trituration with water to give after drying 550 mg (31%) of N-(4-pyridylpropionoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine, mp 78-81°C; NMR ($Me_2SO$) $\delta$ 8.37 (m, 2H), 7,97 (m, 2H), 7.28 to 6.87 (m, 4H), 6.52 (t, 3H), 3.73 to 2.18 (m, 10H), 1.15 (t, 3H).

Example 31

N-(3-Pyridylpropionoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine

0.756 g (5.0 mmol) of 3-pyridylpropionic acid and 0.811 g (5.0 mmol) of 1,1'-carbonyldiimidazole were combined in 25 ml of tetrahydrofuran and heated at reflux until gas evolution ceased. 1.16 g (5.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was added and the reaction was heated at reflux for 2 hours. After cooling the tetrahydrofuran solution was decanted from gummy material in the reaction flask and concentrated in vacuo to an oil. Trituration with water containing a small amount of ethanol gave a solid which was recrystallized from water-methanol to give 0.692 g (38%) of N-(3-pyridylpropionoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl-1',2',4'-triazolyl))ethylamine, mp 124-125°C with decomposition; NMR ($Me_2SO$) $\delta$ 8.27 (m, 2H), 7.93 (m, 2H), 7.5 (m, 1H), 7.2 (m, 1H), 7.0 (m, 2H), 6.5 (t, 1H), 3.67 to 2.2 (m, 10H), 1.13 (t, 3H).

Example 32

N-[4-(4-Imidazolyl)butanoyl]-2-[3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl)]ethylamine hydrochloride

To a slurry of 821 mg (4.31 mmol) of 4-(4-imidazolyl)butanoic acid hydrochloride in 50 ml of acetonitrile was added in one portion 698 mg (4.31 mmol) of 1,1-carbonyldiimidazole and the mixture was heated at reflux under nitrogen for 2 hours. During this time, the mixture became homogeneous. To this was added 1.0 g (4.31 mmol) of 3'-(3-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) and the mixture was heated at reflux for 16 hours. A solid mass had formed and this was broken up in solution. Refluxing was then continued for another 24 hours. The mixture was concentrated, the residue taken up into methanol, then ether was slowly added to allow a solid precipitate fo form. The precipitate was collected by filtration and dried in vacuo to afford 1.14 g (65%) of N-[4-(4-imidazolyl)butanoyl]-2-[3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl)]-ethylamine hydrochloride as a white solid, mp 204-207°C; NMR ($Me_2SO-d_6$) $\delta$ 8.12 (broad t, 1H); 7.90 (d, 1H); 7.52 (s, 1H); 7.33 (s, 1H); 7.07 (d, 1H); 3.6-1.6 (m, 12H); 1.23 (t, 3H). High resolution mass spectrum ($C_{18}H_{28}N_8O$): M/E calcd. 368.2073; found, 368.2098.

Example 33

N-[4-(4-Imidazolyl)propionyl]-2-[3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl)]ethylamine hydrochloride

To a slurry of 761 mg (4.31 mmol) of 3-(4-imidazolyl)propionic acid hydrochloride in 50 ml of acetonitrile was added in one portion 698 mg (4.31 mmol) of 1,1-carbonyldiimidazole and the mixture was heated at reflux under nitrogen for 1.5 hour. To this heterogeneous mixture was added 1.0 g (4.31 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) and the mixture was heated at reflux for 16 hours. The mixture was concentrated leaving an oil which was purified by chromatography over 20 g of "Silica Gel 60" (E. M. Reagents) using 19:1 $CHCl_3/CH_3OH$ as eluent to afford 385 mg (23%) of N-[4-(4-imidazolyl)propionyl]-2-[3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl)]ethylamine hydrochloride as a white foam solid. NMR ($CD_3OD$) $\delta$ 7.90 (d, 1H); 7.61 (s, 2H); 7.32 (s + d, 2H); 3.8-2.5 (m, 10H); 1.40 (t, 3H). High resolution mass spectrum ($C_{17}H_{22}N_8O$): M/E calcd 354.1880; found: 354.1895.

Example 34

N-Nicotinoyl-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine

278 mg (2.26 mmol) of nicotinic acid was added to 15 ml of dry $CH_2Cl_2$ at 0°C and to the stirred slurry was added 0.33 ml (2.37 mmol) of triethylamine and 0.225 ml (2.36 mmol) of ethylchloroformate. After stirring 20 minutes at 0°C, 500 mg (2.15 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was added and the stirred slurry was allowed to warm to 25° and stirred at 25° for 20 hours. The reaction was diluted with aqueous sodium bicarbonate solution and extracted repeatedly

with ethylacetate. The ethyl acetate extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to a crude solid. This material was chromatographed on "Silica Gel 60" (E. M. Reagents) to give 142 mg (20%) of N-nicotinoyl-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine, mp 218-220°C. NMR ($Me_2SO$) $\delta$ 9.04 to 8.55 (m, 3H), 8.27 to 7.83 (2H), 7.47 (m, 1H), 7.05 (m, 2H), 6.53 (t, 1H), 3.93 to 2.8 (m, 6H), 1.15 (t, 3H).

Example 35

N-(Isonicotinoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine

0.492 g (4.0 mmol) of isonicotinic acid was suspended in 50 ml methylene chloride. 0.445 g (4.4 mmol) of triethylamine was added and the reaction was stirred 10 minutes at 25°C and then cooled to 0°C. 0.477 g (4.4 mmol) of ethylchloroformate in 5 ml of methylene chloride was added dropwise over 10 minutes. After 20 minutes stirring, 0.929 g (4.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was added and the reaction was allowed to warm to 25°C and stirred at this temperature for 72 hours. The resulting solid was collected by filtration and recrystallized from water and dried to give 327 mg (24%) of N-(isonicotinoyl)-2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethylamine, mp 213-215°C; NMR ($Me_2SO$) $\delta$ 8.9 (t, 1H), 8.7 (d, 2 x 1H), 8.03 (d, 1H), 7.73 (m, 2H), 7.1 (m, 2H), 6.63 (t, 1H), 3.97 to 2.83 (m, 6H), 1.17 (t, 3H).

Anal. $C_{17}H_{19}N_7O$, Calcd. C, 60.52; H, 5.68; N, 29.06. Found: C, 59.16; H, 5.80; N, 28.50.

Example 36

N-(2-(3'-(5'-(2-Ethylamino-4-pyridyl)-1',2',4'-triazolyl))-ethyl)urea hydrate

1.0 g (4.3 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was dissolved in 4.3 ml (4.3 mmol) of 1N HCl and 10 ml of water. 0.366 g (4.52 mmol) of potassium isocyanate was added. After one hour stirring at 25°C a precipitate began to form. After a total of 18 hours at 25°C the reaction was filtered and the solid filtrate was recrystallized from water and dried to give 540 mg (46%) of N-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethyl)urea hydrate mp 208-211°C. NMR ($Me_2SO$) $\delta$ 8.03 (d, 1H), 7.08 (m, 2H), 6.55 (t, 1H), 6.07 (t, 1H), 5.5 (broad s, 2H), 3.33 (m, 4H), 2.9 (q, 2H), 1.13 (t, 3H).

Anal. $C_{12}H_{17}N_7O \cdot H_2O$, Calcd. C, 49.14; H, 6.52; N, 33.43. Found: C, 49.33; H, 6.34; N, 35.14.

Example 37

N-(2-(3'-(5'-(2-Ethylamino-4-pyridyl)-1',2',4'-triazolyl))-ethyl)-N'-methylurea

0.929 (4.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was dissolved in 20 ml of water. 0.456 g (8.0 mmol) of methylisocyanate was added and the reaction was warmed to 90°C. A solid began to form after 5 minutes and then redissolved after 30 minutes. After one hour at 90°C, the reaction was concentrated in vacuo to an oil which when triturated with acetonitrile gave a solid. This material was collected by filtration and recrystallized from ethanol to give N-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethyl)-N'-methylurea, mp 204-205°C. NMR ($Me_2SO$) $\delta$ 8.0 (d, 1H), 6.87 (m, 2H), 6.5 (t, 1H), 5.97 (t, 1H),

5.0 (q, 1H), 3.67 to 2.7 (m, 6H), 2.53 (d, 3H), 1.15 (t, 3H).

Anal. $C_{13}H_{19}N_7O$, Calcd. C, 53.97; H, 6.62; N, 33.89. Found: C, 53.54; H, 6.54; N, 33.53.

Example 38

N-Cyano-N'N'-dimethyl-N"-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethyl)guanidine sesquihydrate

1.83 g (6.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole bishydrochloride (Example 10) was stirred with 0.829 g (6.0 mmol) of anhydrous potassium carbonate and 40 ml of ethanol and 15 ml of water for 20 minutes. 0.973 g (6.6 mmol) of dimethyl cyanodithioiminocarbonate was added and the reaction was stirred at 25°C for 36 hours at which point a precipitate began to form. After a total reaction time of 48 hours the resultant solid precipitate was collected by filtration and dried to give 1.24 g (63%) N-cyano-N'-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethyl)-S-methylisothiourea, mp 165-166°C with decomposition. An additional 0.6 g was obtained by concentration of the aqueous ethanol mother liquors; NMR ($Me_2SO$) $\delta$ 8.05 (d, 1H), 7.0 (m, 2H), 6.57 (t, 1H), 3.8 to 2.8 (m, 6H), 2.57 (s, 3H), 1.17 (t, 3H).

Anal. $C_{14}H_{18}N_8S$, Calcd. C, 50.89; H, 5.49; N, 33.91. Found: C, 50.70; H, 5.28; N, 33.56.

0.66 g (2.0 mmol) of N-cyano-N'-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethyl)-S-methyl-isothiourea was combined with 15 ml of 40% aqueous dimethylamine and heated at 70°C for 6

hours. The reaction was concentrated in vacuo, an additional 15 ml of 40% aqueous dimethylamine was added and the reaction was heated at reflux for 18 hours. The reaction was concentrated in vacuo, an additional 15 ml of 40% aqueous dimethylamine was added and reflux was continued for 60 hours. The reaction was concentrated in vacuo and triturated with acetonitrile and the resultant solid was collected by filtration to give 250 mg (53%) of N-cyano-N'N'-dimethyl-N"-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethyl)guanidine sesquihydrate mp 87°C with decomposition. NMR ($Me_2SO$) $\delta$ 8.03 (d, 1H), 7.07 (m, 3H), 6.57 (t, 1H), 3.9 to 2.83 (m, 6H), 3.0 (s, 6H), 1.17 (t, 3H).

Anal. $C_{15}H_{21}N_9 \cdot 1.5H_2O$, Calcd. C, 50.83; H, 6.82; N, 35.57. Found: C, 50.92; H, 6.39; N, 35.44.

Example 39

N-Cyano-N'-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethyl)-N"-methylguanidine

1.03 g (3.1 mmol) of N-cyano-N'-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethyl)-S-methylisothiourea (Example 36) was combined with 30 ml of 40% aqueous methylamine to give a yellow solution and kept at 25°C for 4 hours. Concentration in vacuo gave a crude solid which was recrystallized from dimethylformamide-water to give 557 mg (57%) of N-cyano-N'-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))-ethyl-N"-methylguanidine, mp 244-246°C; NMR ($Me_2SO$) $\delta$ 8.07 (d, 1H), 7.12 (m, 2H), 6.57 (t, 1H), 3.77 to 2.83 (m, 6H), 2.73 (d, 3H), 1.18 (t, 3H).

Anal. $C_{14}H_{19}N_9$, Calcd. C, 53.66; H, 6.11; N, 40.23. Found: C, 53.28; H, 6.22; N, 40.15.

Example 40

N-[3'-(5'-(2-ethylamino-4-pyridyl))-1',2',4'-triazolyl]methyl N'-methyl-thiourea hydrochloride hemihydrate

To a solution of sodium methoxide prepared from 150 mg (6.5 mmol) of sodium pellets in 100 ml of methanol was added 6.9 g (50 mmol) of 2-chloroisonicotinonitrile. The reaction was stirred at 25°C for 1.5 hours and 6.6 g (50 mmol) of hydantoic acid hydrazide was added and the reaction was heated at reflux for 60 hours. The resultant solid was collected by filtration and dried to give 7.6 g (53%) of N-(2-chloro-isonicotinimidoyl)-N'-ureidomethylcarbonyl hydrazine hydrate mp 196-197°C with gas evolution. NMR ($Me_2SO$) $\delta$ 8.37 (d, 1H), 7.73 (m, 2H), 6.67 (broad s, 2H), 6.06 (t, 1H), 5.66 (broad s, 2H), 4.12 (d, 2H).

Anal. $C_9H_{11}ClN_6O_2 \cdot H_2O$, Calcd. C, 36.72; H, 4.86; N, 29.11; Cl, 13.10. Found: C, 36.72; H, 4.86; N, 28.89; Cl, 11.41.

7.5 g (25.98 mmol) of N-(2-chloro-isonicotinimidoyl)-N'-ureidomethylcarbonyl hydrazine hydrate was combined with 150 ml 70% aqueous ethylamine in a 300 ml stainless steel pressure vessel and heated at 170°C for 96 hours. After cooling the reaction contents were concentrated in vacuo to a heavy oily solid. This mixture was triturated with isopropyl alcohol. Filtration gave a grey-white solid which was treated with activated charcoal and recrystallized from isopropyl alcohol-methanol to give 0.87 g (13%) of 3'-aminomethyl-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole hydrochloride, mp 220-223°C; NMR ($Me_2SO$) $\delta$ 8.95 (broad s, 3H), 8.03 (d, 1H), 7.07 (m, 3H), 4.17 (broad s, 2H), 3.27 (m, 2H), 1.15 (t, 3H).

Anal. $C_{10}H_{14}N_6HCl$, Calcd. C, 47.14; H, 5.93; N, 32.99. Found: C, 47.63; H, 5.82; N, 33.16.

500 mg (1.96 mmol) of 3'-aminomethyl-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole hydrochloride was combined with 0.2 ml (2.92 mmol) of methylisothiocyanate in 7 ml $H_2O$ and heated at reflux for 3 hours. The reaction was concentrated in vacuo to a glass which was recrystallized from ethylacetate-methanol to give 390 mg (59%) of N-[3'-(5'-(2-ethylamino-4-pyridyl))-1',2',4'-triazolylmethyl-N'-methyl-thiourea hydrochloride hemihydrate, loss of water at 102°, mp 232°. High resolution mass spectrum ($C_{12}H_{17}N_7S$) M/E Calcd. 291.1266. Found 291.1272.

Anal. $C_{12}H_{17}N_7S \cdot HCl \cdot 1/2H_2O$, Calcd. C, 42.78; H, 5.68; N, 29.10. Found: C, 42.74; H, 5.38; N, 28.96.

Example 41

N'-(2-(3'-(5'-(2-Ethylamino-4-pyridyl)-1',2',4'-triazolyl))-ethyl)-N'-methylthiourea

0.806 g (2.6 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole bishydrochloride (Example 10) was combined with 0.415 g (3.0 mmol) of anhydrous potassium carbonate and 0.22 g (3.0 mmol) of methylisothiocyanate in 30 ml of water and heated at reflux for 18 hours. On cooling a solid formed and was collected by filtration and recrystallized from water to give 0.3 g (39%) of N'-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethyl)-N'-methylthiourea, mp 189-191°C; NMR ($Me_2SO$) $\delta$ 7.98 (d, 1H), 7.43 (t, 2 x 1H), 7.03 (m, 2H), 4.0 to 2.92 (m, 6H), 2.8 (d, 3H), 1.13 (t, 3H).

Anal. $C_{13}H_{19}N_7S$, Calcd. C, 51.13; H, 6.27; N, 32.10. Found: C, 50.96; H, 6.17; N, 32.16.

Example 42

N'-(4-(3'-(5'-(2-Ethylamino-4-pyridyl)-1',2',4'-triazolyl))-butyl)-N'-methylthiourea

18.4 g (59.2 mmol) of ethyl 5-phthalimidopentanimidate hydrochloride (prepared from 13.5 g (59.2 mmol) of 5-phthalimidopivalonitrile was combined with 59.2 mmol of sodium ethoxide (prepared from 1.36 g (59.2 mmol) of sodium pellets in 250 ml of ethanol. After stirring at 25°C for 5 minutes, 8.0 g (44.4 mmol) of 2-ethylaminoisonicotinic acid hydrazide was added and the reaction was heated at reflux for 18 hours. The reaction was cooled and the resultant precipitate was collected by filtration and then slurried in water and the resultant solid was collected by filtration and dried to give 10.8 g (62%) of 3'-(4-phthalimidobutyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole mp 166-168°C. An additional 5.8 g mp 163-165°C was obtained by workup of the original ethanol mother liquors.

14.51 g (37.2 mmol) of 3'-(4-phthalimidobutyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole was combined with 2 ml (41.0 mmol) of hydrazine hydrate in 300 ml ethanol and heated at reflux. Solution occurred in about 10 minutes and after 1.5 hours a solid began to form. After a total of 3 hours at reflux the reaction was cooled and concentrated in vacuo. The resultant solid was slurried in 400 ml water made acidic with 2.3 N hydrochloric acid. The slurry was filtered and the clear aqueous solution was concentrated in vacuo to a yellow solid. This material was recrystallized from 140 ml methanol to give 8.1 g (65%) of 3'-(4-aminobutyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole trihydrochloride, mp 283-285°C with decomposition.

NMR ($D_2O$) $\delta$ 7.9 (d, 1H), 7.42 (broad s, 1H), 7.25 (d of d, 1H), 3.43 (q, 2H), 3.12 (m, 4H), 1.96 (m, 4H), 1.42 (t, 3H).

Anal. $C_{13}H_{20}N_6 \cdot 3HCl$, Calcd. C, 42.23; H, 6.27; N, 22.73. Found: C, 41.68; H, 5.99; N, 22.79.

1.0 g (2.7 mmol) of 3'-(4-aminobutyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole trihydrochloride was combined with 0.417 g (3.0 mmol) of anhydrous potassium carbonate, 0.439 g (6.0 mmol) of methyl isothiocyanate and 15 ml of water and heated at reflux for 3 hours. A small amount of ethanol was used to wash sublimed methylisothiocyanate from the condenser into the reaction flask and reflux was continued for an additional 4 hours. The reaction was concentrated in vacuo and the resultant oily solid was slurried in ethanol and the insoluble salts removed by filtration. The ethanol solution was reconcentrated in vacuo and chromatographed on "silica gel 60" (E. Merck) using 10% methanol in chloroform as eluent to give product as an oil which solidified on standing. This material was triturated with acetonitrile. The resultant solid was collected by filtration and recrystallized from acetonitrile to give 0.163 g (18%) of N-(4-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))butyl)-N'-methylthiourea, mp 159-161°C; NMR ($Me_2SO$) $\delta$ 7.98 (d, H), 7.33 (m, 2H), 7.0 (m, 2H), 6.48 (t, 1H), 3.3 (m, 6H), 2.77 (d, 3H), 1.6 (m, 4H), 1.1 (t, 3H).

Anal. $C_{15}H_{23}N_7S$, Calcd. C, 54.03; H, 6.95; N, 29.40. Found: C, 53.91; H, 6.66; N, 29.39.

Example 43

N-(2-(3'-(5'-(2-Ethylamino-4-pyridyl)-1',2',4'-triazolyl))-ethyl)-N'-methyl-2-nitro-1,1-ethenediamine

0.929 g (4.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) and 0.593 g (4.0 mmol) of N-methyl-1-methylthio-2-nitro-ethenamine were combined in 30 ml of ethanol and heated at reflux for 7 hours. The ethanol was removed by distillation and replaced by an equal volume of iso-amyl alcohol and reflux was continued for 18 hours. The reaction was concentrated in vacuo and the resultant oily solid was chromatographed on "silica gel 60" (E. Merck) using 10% methanol in chloroform as eluent to give 280 mg (21%) of N-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))ethyl-N'-methyl-2-nitro-1,1-ethenediamine, mp 223-224°C with decomposition; NMR ($Me_2SO$) $\delta$ 7.98 (d, 1H), 7.0 (m, 2H), 6.53 (t, 1H), 6.45 (s, 1H), 3.8 to 2.83 (m, 6H), 2.73 (d, 3H), 1.12 (t, 3H).

Anal. $C_{14}H_{20}N_8O_2$, Calcd. C, 50.59; H, 6.07; N, 33.71. Found: C, 50.65; H, 6.11; N, 32.01.

Example 44

2-(2-(3'-(5'-(2-Ethylamino-4-pyridyl)-1',2',4'-triazolyl))-ethylamino)-6-methylpyrimidin-4-one hemihydrate

929 mg (4.0 mmol) of 3'-(2-aminoethyl)-5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazole (Example 10) was combined with 625 mg (4.0 mol) of 2-methylthio-6-methyl-pyrimidin-4-one and warmed at 170°C. Gas evolution ceased after about 1.5 hours. After cooling, methanol was added to give a crude solid which was collected by filtration and then slurried in water. The solid was refiltered, washed with methanol and then ether and dried to give 840 mg (60%) of

2-(2-(3'-(5'-(2-ethylamino-4-pyridyl)-1',2',4'-triazolyl))-ethylamino)-6-methyl-pyrimidin-4-one hemihydrate, mp 178-181°C with decomposition. NMR ($Me_2SO$) $\delta$ 8.06 (d, 1H), 7.02 (m, 2H), 6.58 (t, 2 x 1H), 5.45 (s, 1H), 3.9 to 2.8 (m, 6H), 2.07 (s, 3H), 1.17 (t, 3H). Anal. $C_{16}H_{20}N_8O.1/2H_2O$, Calcd. C, 55.00; H, 6.06; N, 32.07. Found: C, 54.70; H, 6.27; N, 31.72.

Example 45

The gastric antisecretory activity of compounds of the present invention was determined in overnight fasted, conscious Heidenhain pouch dogs. Pentagastrin (Peptavlon-Ayerst) was used to stimulate acid output by continuous infusion into a superficial leg vein at doses earlier determined to stimulate near maximal acid output from the gastric pouch. Gastric juice was collected at 30 minute intervals following the start of a pentagastrin infusion and measured to the nearest 0.1 ml. Ten collections were taken for each dog during an experiment. Acid concentration was determined by titrating 1.0 ml of gastric juice to pH 7.4 with 0.1N sodium hydroxide using an Autoburette and a glass electrode pH meter (Radiometer).

Drug or vehicle was given intravenously 90 minutes following the start of the pentagastrin infusion, at a dose of 1 mg/kg. Gastric acid antisecretory effects were calculated by comparing the lowest acid output after drug administration with the mean acid output immediately before drug.

The results obtained are as follows:

1. Compounds of Examples #2, 3, 8, 12, 17, 20, 21, 24, 26, 27, 31, 35 and 36 gave greater than 50% inhibition of acid secretion in dogs at doses of 10 mg/kg or less.

2. The compounds of Examples #12 and 41 gave greater than 50% inhibition of acid at a dosage of 1 mg/kg.

Example 46

The histamine-$H_2$ antagonist activity of compounds of the present invention was determined by the following procedure:

Guinea pigs are killed rapidly with a blow to the head, the heart removed and the right atria dissected free. Atria are suspended, isometrically, in a temperature-controlled (32°±2°) tissue bath (10 ml) containing oxygenated (95% $O_2$; 5% $CO_2$) Krebs-Henseleit buffer (pH 7.4) and are allowed to stabilize approximately one hour during which time the tissue bath is flushed several times. Individual atrial contractions are followed with a force-displacement transducer connected to a cardiotachometer and Grass polygraph recorder. After obtaining a dose-response curve to histamine, the bath containing each atrium is flushed several times with fresh buffer and the atria re-equilibrated to basal rates. Following the return to basal rate, test compounds are added at selected final concentrations and the histamine dose-response curve is again determined in the presence of antagonist. Results are expressed as dose-ratios, the ratio of histamine concentrations required to produce one-half of maximal stimulation in the presence and absence of antagonist, and the apparent dissociation constant of the $H_2$-receptor antagonist $pA_2$ is determined. The results obtained are as follows:

1. Compounds of Examples #2, 3, 6, 28, 29, 31, 32, 34, 39 and 41 gave $pA_2$ values of 6.0 or greater.

2. Compounds of Examples #5, 8, 11, 13-27, 30, 33, 35-38, 40 and 43 gave $pA_2$ values between 5.0 and 6.0.

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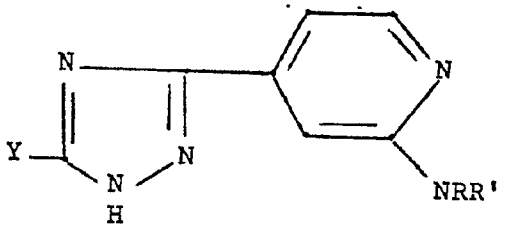
## CLAIMS

1. A compound of the formula



---(I)

or a pharmaceutically acceptable salt thereof, wherein R is alkyl and R' is hydrogen, methyl or ethyl; and

Y is hydrogen, hydroxymethyl, alkyl or $-(CH_2)_nNHC(Z)Q$

wherein n is an integer from 1 to 4; and

Z and Q, when taken together, form a 4-pyrimidinone group; or when taken separately, Z is oxygen, sulfur, =N-C≡N, or $=(CH)NO_2$; and Q is -CH=CHR" wherein R" is 2-methyl-5-thiazolyl, 4-pyridyl or 4-imidazolyl; or

Q is $-(CH_2)_mR"'$, wherein R"' is hydrogen, alkyl, thioalkoxy, alkoxy, amino, N-monoalkylamino, N,N-dialkylamino, 2-guanidino-4-thiazolyl, 5-dimethylaminomethyl-2-furyl, 2-pyrazinyl, 4-imidazolyl, 5-methyl-4-imidazolyl, phenyl, mono-substituted phenyl, 3-pyridyl, mono-substituted 3-pyridyl, 4-pyridyl, or mono-substituted 4-pyridyl, wherein said substituents are halo, alkoxy, hydroxy or alkylamino; and

m is 0 or an integer from 1 to 3;

provided that when R"' is hydrogen, alkoxy, phenoxy or pyridoxy, m is other than 0; said alkyl, alkoxy, and thioalkoxy groups having from 1 to 4 carbon atoms.

2. A compound of claim 1 wherein n is 2, R is ethyl or methyl and R' is hydrogen.

3. A compound of claim 2 wherein Y is hydrogen, hydroxymethyl or alkyl.

4. A compound of claim 1 wherein Z is oxygen and Q is -CH=CHR" wherein R" is 2-methyl-4-thiazolyl, 4-pyridyl or 4-imidazolyl or Q is alkyl, amino, methylamino, 2-guanidino-4-thiazolyl, 5-dimethylamino-methyl-2-furyl, 2-pyrazinyl, phenyl, substituted phenyl, 3-pyridyl, substituted 3-pyridyl, 4-pyridyl or substituted 4-pyridyl wherein said substituents are halo, alkoxy, hydroxy or alkylamino or Q is $-CH_2R'''$ wherein R''' is alkoxy, phenoxy, 3-pyridyloxy or 4-pyridyl or Q is $-(CH_2)_2R'''$ wherein R''' is phenyl or 3-pyridyl or Q is $-(CH_2)_3R'''$ wherein R''' is 4-imidazolyl or 5-methyl-4-imidazolyl.

5. A compound of claim 1 wherein Z is sulfur and Q is N-alkylamino.

6. A compound of claim 1 wherein Z is =N-C≡N, and Q is thioalkyloxy, N-alkylamino or N,N-di-alkylamino.

7. A compound of claim 1 wherein Z is $=CHNO_2$ and Q is N-alkylamino.

8. A compound of claim 1 wherein Z and Q when taken together form a 6-methylpyrimidin-4-one group.

9. A pharmaceutical composition comprising a compound of the formula (I) as claimed in any one of the preceding claims, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

10. A compound of the formula (I) as claimed in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use in treating a condition caused or aggravated by hyperacidity in a human being.

11. A process for preparing a compound of the formula (I) as claimed in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, substantially as described herein.

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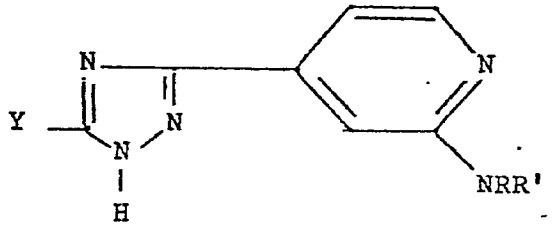
CLAIMS FOR AUSTRIA

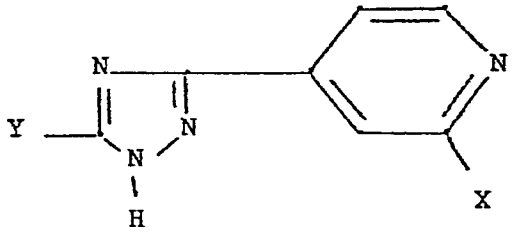
1. A process for preparing a compound of the formula



(I)

wherein Y is hydrogen, hydroxymethyl or alkyl having from 1 to 4 carbon atoms; R is $C_1$-$C_4$ alkyl; R' is hydrogen, methyl or ethyl;

characterized in that a compound of the formula

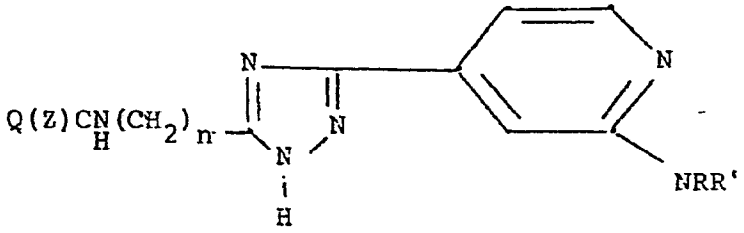


wherein X is halo

is contacted with an alkylamine of the formula HNRR' where R and $R^1$ are as defined above and, optionally, converting the compound of formula I to a pharmaceutically acceptable salt.

2. A process as claimed in claim 1, which is carried out in aqueous media.

3. A process for preparing a compound of the formula



wherein R is alkyl, R' is hydrogen, methyl or ethyl, n is an integer from 1 to 4; and

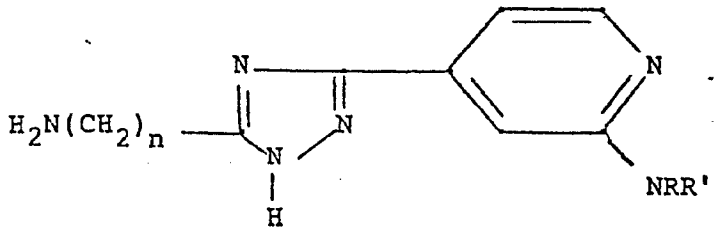
Z and Q, when taken together, form a 4-pyrimidinone group; or when taken separately, Z is oxygen, sulfur or $=CH(NO_2)$; and Q is -CH=CHR" wherein R" is 2-methyl-5-thiazolyl, 4-pyridyl or 4-imidazolyl; or

Q is $-(CH_2)_nR'''$, wherein R''' is hydrogen, alkyl, thioalkoxy, alkoxy, amino, N-monoalkylamino, phenoxy, pyridyloxy, N,N-dialkylamino, 2-guanidino-4-thiazolyl, 5-dimethylaminomethyl-2-furyl, 2-pyrazinyl, 4-imidazolyl, 5-methyl-4-imidazolyl, phenyl, mono-substituted phenyl, 3-pyridyl, mono-substituted 3-pyridyl, 4-pyridyl or mono-substituted 4-pyridyl, wherein said substituents are halo, alkoxy, hydroxy or alkylamino; and

n is 0 or an integer froml to 3;

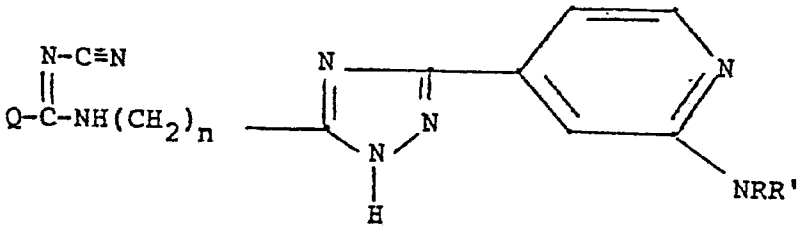
provided that when R''' is hydrogen, alkoxy, phenoxy or pyridyloxy, n is other than 0; said alkyl, alkoxy and thioalkoxy groups having from 1-4 carbon atoms;

characterized in that a compound of the formula



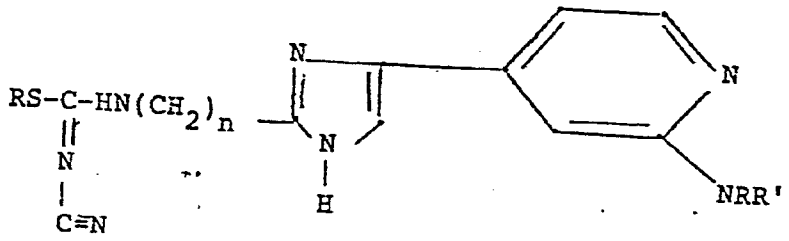

is reacted with an appropriate carboxylic acid, carboxylic acid chloride, isocyanate, alkyl isocyanate, isothiocyanate, alkyl isocyanate, N-alkyl-1-alkylthio-2-nitroetheneamine or alkylthiopyrimidinone.

4. A process for preparing a compound of the formula



wherein R is $C_1$-$C_4$ alkyl, R' is hydrogen, methyl or ethyl, n is an integer from 1 to 4 and Q is amino, N-alkylamino or N,N-dialkylamino said alkyl having from 1-4 carbon atoms;

characterized in that a compound of the formula



wherein R is alkyl having from 1 to 4 carbon atoms

is reacted with an amine of the formula QH where Q is as defined above.

European Patent Office

# EUROPEAN SEARCH REPORT

0074229
Application number

EP 82 30 4531

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl. ³) |
|---|---|---|---|
| A,D | GB-A-2 053 910 (PFIZER)<br>*Claims; page 15* | 1,9,10,11 | C 07 D 401/04<br>C 07 D 401/14<br>C 07 D 417/14<br>C 07 D 405/14<br>A 61 K 31/00 |

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

C 07 D 401/00
C 07 D 417/00
C 07 D 405/00

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| THE HAGUE | 28-12-1982 | CREMERS K. |

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